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The American Journal of Medicine

Vol. XIV JANUARY, 1953 No. 1

Editorial

Clinical Studies

The authors describe the clinical and cardiac catheterization findings in ten proven and seven probable cases of interatrial septal defect, stressing in particular the pitfalls encountered if the catheter is not passed through the defect. When interatrial septal defect is the sole anomaly, the findings depend in large measure, of course, on whether the shunt is predominantly from left to right or from right to left, according to the pressure gradient between the atria. How the direction of flow affects the clinical findings is brought out interestingly.

This study brings out a number of important practical points in the management of patients with emphysema in whom acute anoxia, cardiac failure and respiratory acidosis supervene as a result of superimposed bronchial infection often not accompanied by fever or leukocytosis. The dangers of uncontrolled oxygen therapy under these circumstances and the advantages of concomitant artificial respiration are pointed out.

Pulmonary function studies in patients with bronchial asthma between attacks, and ostensibly quite normal, reveal a surprising degree of impairment in performance of certain pulmonary function tests such as maximum breathing capacity. The results of such tests, described in detail in the first of these two papers, imply a substantial residue of persistent bronchospasm and emphysema in many asthmatics in symptom-free periods. The second paper describes the effects of intravenous aminophyllin and bronchodilator aerosols. Some tests reflect the beneficial effects of bronchodilation, others indicate failure to influence the more permanent changes in the lungs.

Contents continued on page 5

*in musculoskeletal pain

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prompt · prolonged · prescribed

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The American Journal of Medicine

Vol. XIV JANUARY, 1953 No. 1

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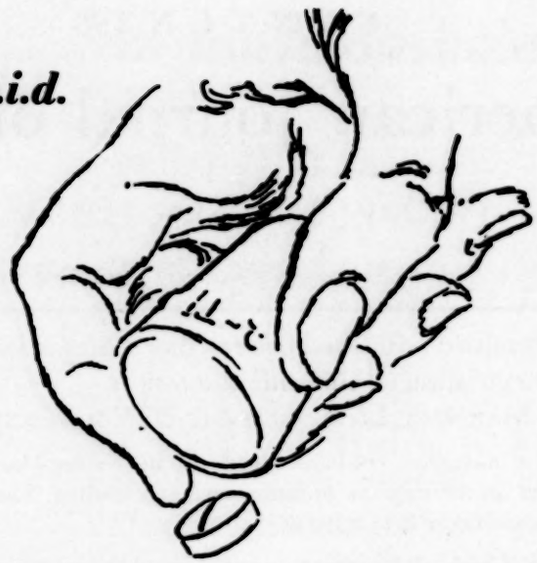
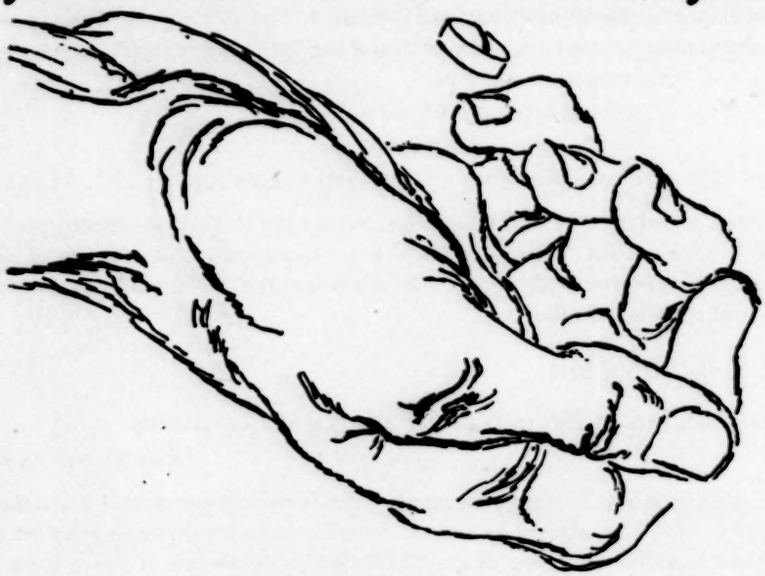
oral penicillin t.i.d.



. . . for the more common bacterial infectious diseases



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CONTENTS

The American Journal of Medicine

Vol. XIV JANUARY, 1953 No. 1

Contents continued from page 5

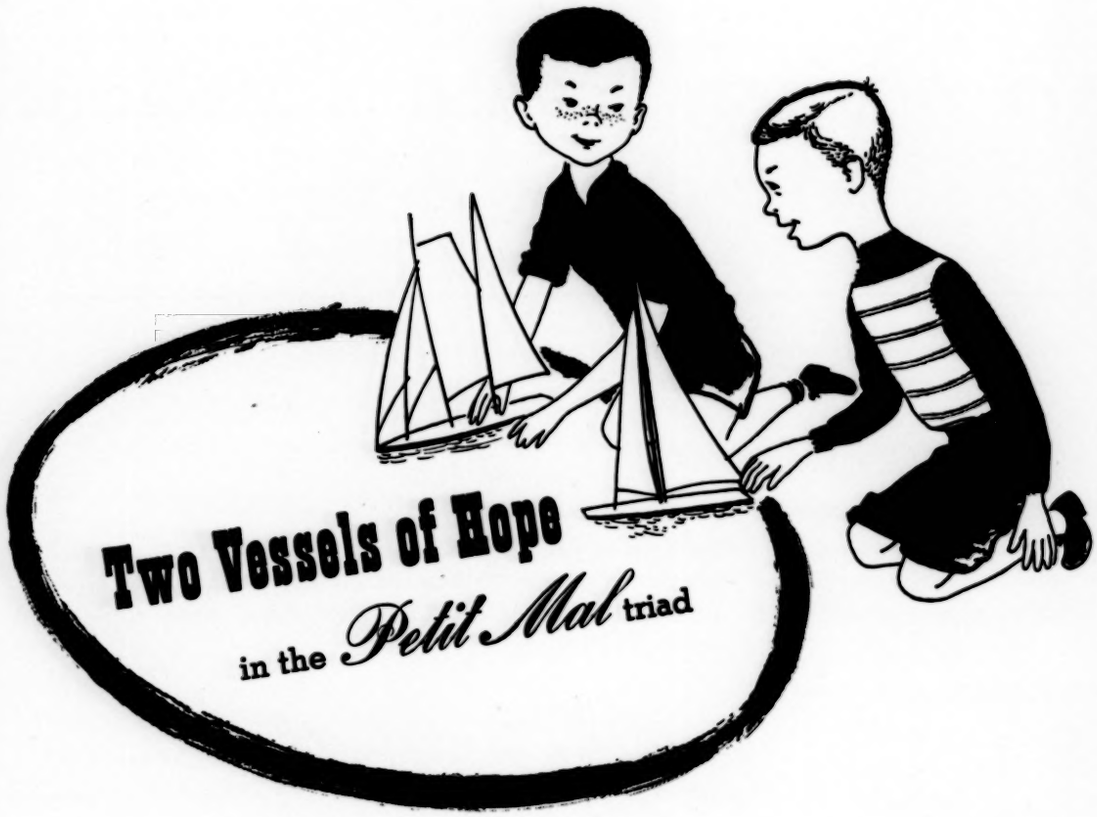
brings out. In some situations cough should be encouraged, not suppressed; in others treatment should be given but varied according to cause and objective.

Clinico-pathologic Conference

Case Reports

Advertising Index on 3rd Cover

Change of address must reach us one month preceding month of issue.



Two Vessels of Hope

in the *Petit Mal* triad

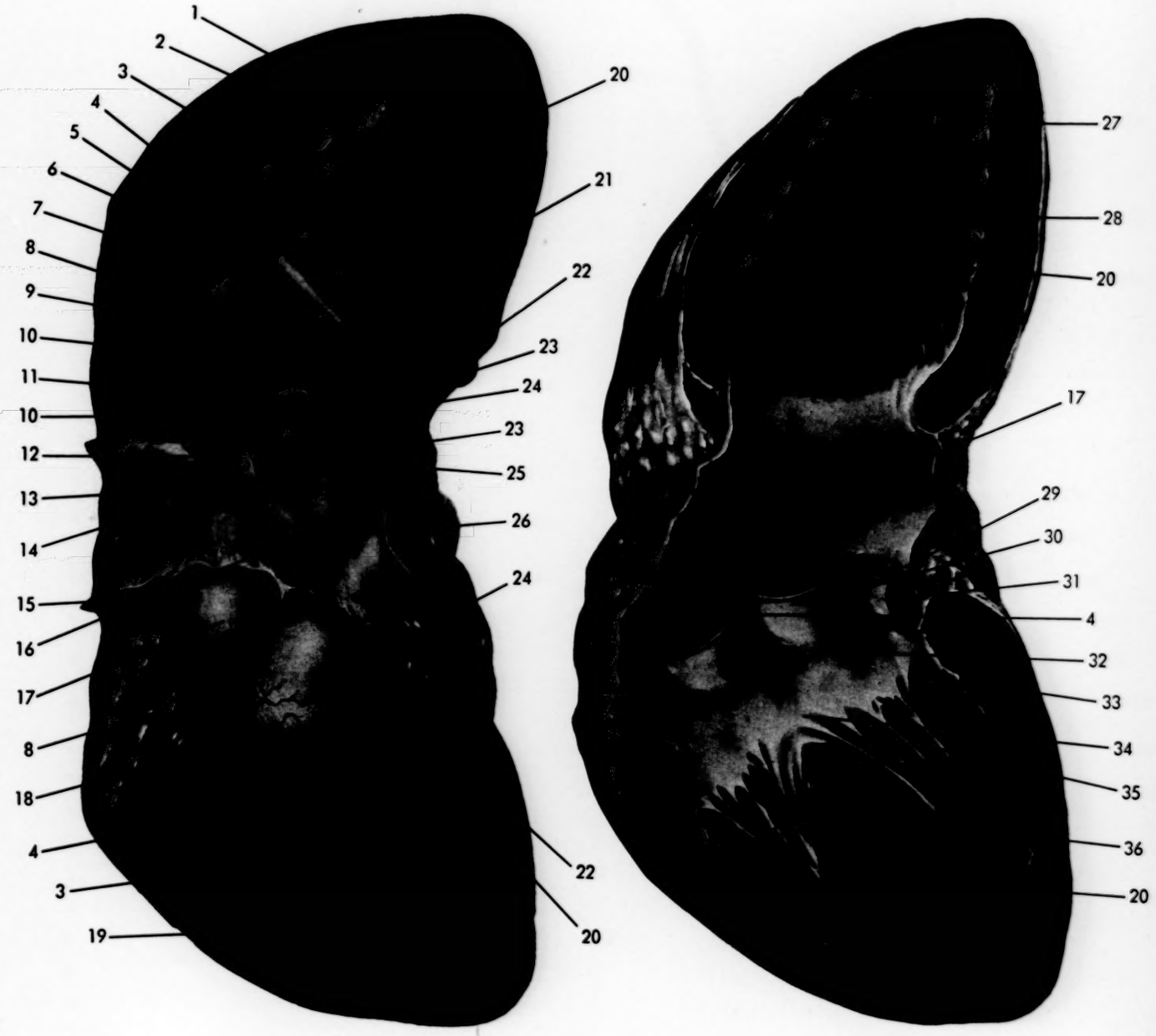
FROM the nightmarish world of constant seizures to a happy, normal life is the opportunity TRIDIONE and PARADIONE offer to many little victims of *petit mal.* The two drugs—products of Abbott's extensive, continuing search for anticonvulsants—already have been dramatically effective in the symptomatic control of *petit mal,* myoclonic jerks and akinetic seizures. • *One drug may prove successful when the other has failed.* That is the one important variation investigators have discovered in TRIDIONE and its homologue, PARADIONE. Relief for a child is still possible if one of the two agents remains untried. • However, *please* do not administer either drug until you have familiarized yourself with the necessary precautions and techniques. Write today to Abbott Laboratories, North Chicago, Ill., for detailed information. Both drugs are available at pharmacies. Abbott

Tridione

Paradione

1-79

Anatomy *of the* Heart



1 Middle cardiac vein
2 Posterior descending branch of right coronary artery
3 Right ventricle
4 Right coronary artery
5 Small cardiac vein
6 Inferior vena cava
7 Coronary sinus
8 Right auricle
9 Left atrium
10 Right pulmonary vein
11 Right branch of pulmonary artery
12 Innominate artery
13 Superior vena cava
14 Left common carotid artery
15 Pericardium
16 Aortic arch
17 Ascending aorta
18 Conus arteriosus
19 Anterior descending branch of left coronary artery
20 Left ventricle
21 Posterior vein of left ventricle
22 Great cardiac vein
23 Left pulmonary vein
24 Left auricle
25 Left subclavian artery
26 Left branch of pulmonary artery
27 Trabeculae carneae
28 Trabecula tendinea
29 Left coronary artery
30 Posterior semilunar valve
31 Left semilunar valve
32 Right semilunar valve
33 Posterior cusp of mitral (bicuspid) valve
34 Anterior cusp of mitral (bicuspid) valve
35 Chordae tendineae
36 Papillary muscle

This is one of a series of paintings by Paul Peck, illustrating the anatomy of various organs and tissues of the body which are frequently attacked by infection, where aureomycin may prove useful.

Aureomycin

HYDROCHLORIDE CRYSTALLINE

in

Infections Involving the Heart

ENDOCARDITIS—Aureomycin has established itself as one of the most valuable agents available for the treatment of infections involving the heart. Aureomycin is now recognized as a highly effective antibiotic against the organisms most frequently encountered in endocarditis—staphylococci, *Str. viridans*, *Str. fecalis* and other enterococci. These organisms are being increasingly found resistant to penicillin and streptomycin. Endocarditis caused by these organisms has responded to aureomycin after failure of other antibiotics. Aureomycin is held by many physicians to be an antibiotic of choice for prophylactic use in patients with organic cardiac disease who require oral, intestinal, or rectal surgery, or any transurethral operative procedure. Endocarditis complicating typhus and brucellosis has responded well to aureomycin therapy.

PERICARDITIS—The importance of aureomycin in pericarditis has been demonstrated by its successful use after failure of other therapy—in acute nonspecific pericarditis, possibly of viral etiology; *H. influenzae* pericarditis; tularemic pericarditis; and actinomycotic pericarditis.

RHEUMATIC FEVER—Because aureomycin is an antibiotic with a wide range of effectiveness against the pathogenic strains of streptococci, its use has been recommended for the prevention of acute rheumatic fever and its cardiac complications.

* * *

PACKAGES: *Capsules:* 50 mg.–Vials of 25 and 100; 100 mg.–Vials of 25 and bottles of 100; 250 mg.–Vials of 16 and bottles of 100. *Ophthalmic Solution:* Vials of 25 mg.; solution prepared by adding 5 cc. distilled water.

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LATE FINDINGS
on the value of CITRUS

Where?	Why?	How?	References
in ABORTION	to help mitigate formation of hematomas in Rh-negative mothers; and in toxemias	citrus fruits and their concentrates and vitamin C supplement	Surg., Gynec. & Obst. 94:257, 1952
in ALCOHOLISM	to force fluids; and help assure adequate nutrition	vitamin C orally in large doses after acute stage has been brought under control	Virginia M. Month. 79:70, 1952
in AVIATION MEDICINE	to replenish vitamin C lost in hypoxemia or hyper-ventilation; and provide quick energy	liberal quantities of fruit or fruit juices	J. Aviation Med. 21:283, 1950; Mil. Surg. 108:125, 1951
in BURNS	to improve nutrition prior to grafting; and promote healing	large doses of vitamin C as soon as patient can eat	Am. J. Surg. 83:746, 1952; GP 5:35, 1952
in OBESITY	to appease appetite during reducing; and combat hypoglycemia	50 calories of citrus fruit (e.g. 4 oz. fresh orange juice) before lunch and dinner	Postgrad. Med. 9:106, 1951
in PEPTIC ULCER	to avoid vitamin C deficiency; aid healing and assist in weight control	2-3 oz. strained citrus fruit juice in water (or milk) at end of meal	Sandweiss: "Peptic Ulcer," 1951; "Low Cost Therapeutic Diets," 1952
in RHEUMATIC CONDITIONS	to maintain good nutrition without obesity; provide purine-free food; and help reduce inflammation	for arthritis, high-vitamin diet; for rheumatic fever, orange juice 200 mg. daily; for gout, diet prominent in fruits, including citrus	Am. Pract. 2:577, 1951; "Current Therapy," 1952

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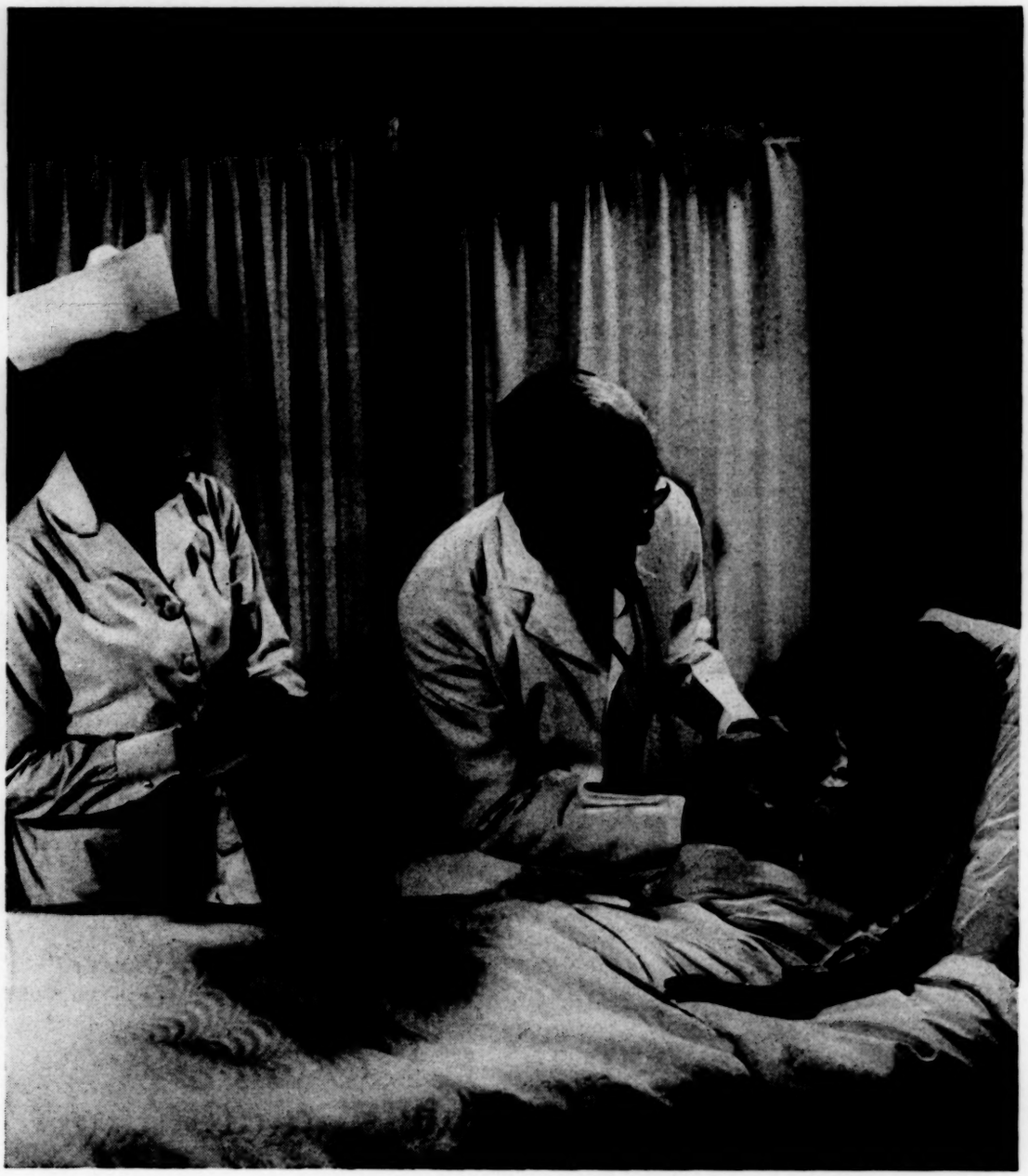
FLORIDA Citrus

ORANGES • GRAPEFRUIT • TANGERINES

Expressed in panel discussion:[1]



Except for the most severe infections, oral penicillin, in the form of PENALEV *Tablets, "eliminates the needle" in treating bacterial pneumonia, tonsillitis, scarlet fever and many other bacterial diseases, in both children and adults.*

Preference for Oral Penicillin

A highlight of the 101st Annual Session of the Medical Society of the State of Pennsylvania was a panel discussion of the more important new drugs used in internal medicine.

Initially, the discussion centered around the treatment of bacterial pneumonia with various antibacterials. One of the panel members remarked that "we give penicillin by mouth . . . we prefer to give it by mouth."[1] Other panel members were in agreement that penicillin is the drug of choice. "The temperature responses in the various groups (given other, costlier antibiotics)—illustrate the point that oral penicillin is as effective . . ."[1]

Less Sensitivity With Oral Penicillin?

There is now no question of the effectiveness of oral penicillin except in the most refractory infections, such as subacute bacterial endocarditis. Furthermore, many clinicians are of the impression that, "there is less sensitivity to penicillin when it is given by mouth . . . than by the hypodermic method."[1]

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CRYSTALLINE POTASSIUM
PENICILLIN G

1. Panel Discussion, Pennsylvania M.J., *55*:42, Jan., 1952

PENALEV *Soluble Tablets Crystalline Potassium Penicillin G are supplied in 3 potencies; 50,000 units, 100,000 units, and 250,000 units, packages of 12 and 100 Tablets. Sharp & Dohme, Philadelphia 1, Pa.*

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new... synthetic...

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Journal of the American Medical Association 149:*729 (June 21) 1952.*

Kuzell, W. C., and others: Phenylbutazone (Butazolidin®) in Rheumatoid Arthritis and Gout.

Gout: "... 25 of the 48 gouty patients experienced a complete remission in 48 hours or less."

Journal of the American Medical Association 150:*1087 (Nov. 15) 1952.*

Steinbrocker, O., and others: Phenylbutazone Therapy of Arthritis and Other Painful Musculoskeletal Disorders.

Osteoarthritis: In 63 per cent "... there was improvement of functional capacity ranging from slight to complete, with striking enhancement of coordinated movements...."

Journal of the American Medical Association 150:*1084 (Nov. 15) 1952.*

Stephens, C. A. L., Jr., and others: Benefits and Toxicity of Phenylbutazone (Butazolidin®) in Rheumatoid Arthritis.

Spondylitis: "Of the 32 patients ... 25 patients (80%) showed 3 to 4 plus subjective improvement."

Bulletin on Rheumatic Diseases 3:*23, 1952.*

Kuzell, W. C.: Phenylbutazone (Butazolidin®).

Rheumatoid arthritis: "Its use is followed by substantial relief of symptoms in about 80 per cent of patients with rheumatoid arthritis."

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department of Geigy Pharmaceuticals

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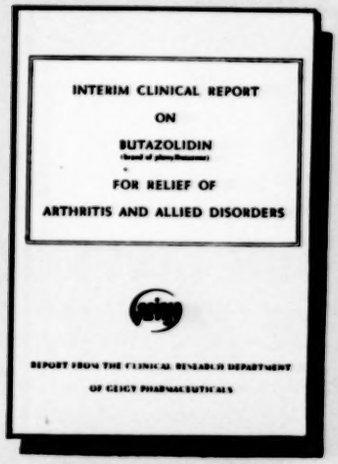

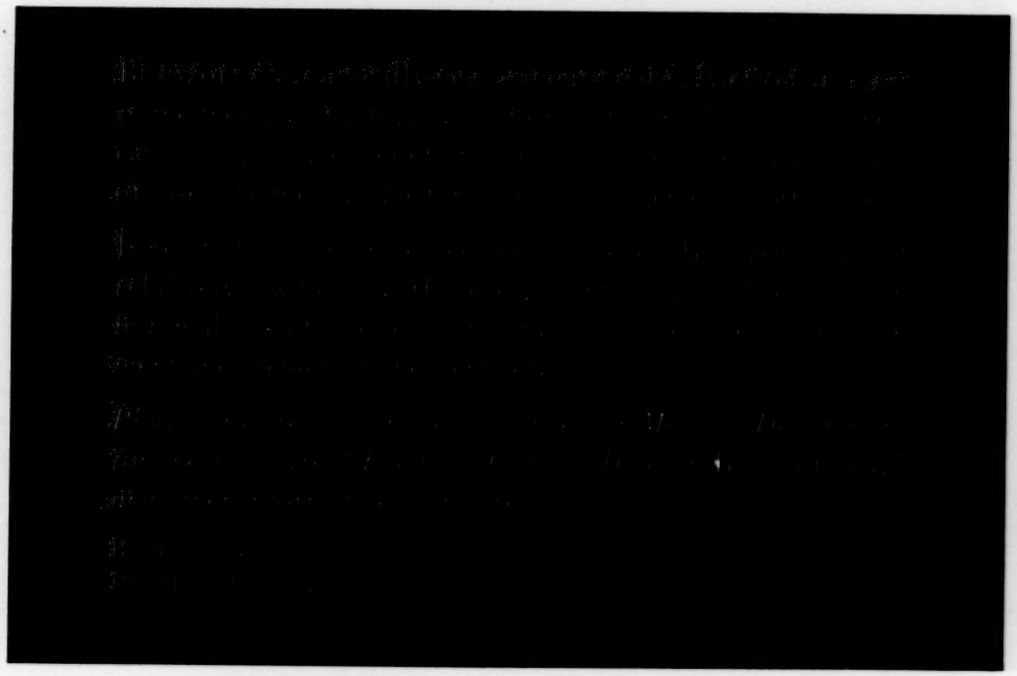

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*Talkov, R. H., Ropes, M. W., and Bauer, W.: *The Value of Enteric Coated Aspirin.* N.E.J. Med. 242,19 (Jan. 5) 1950.

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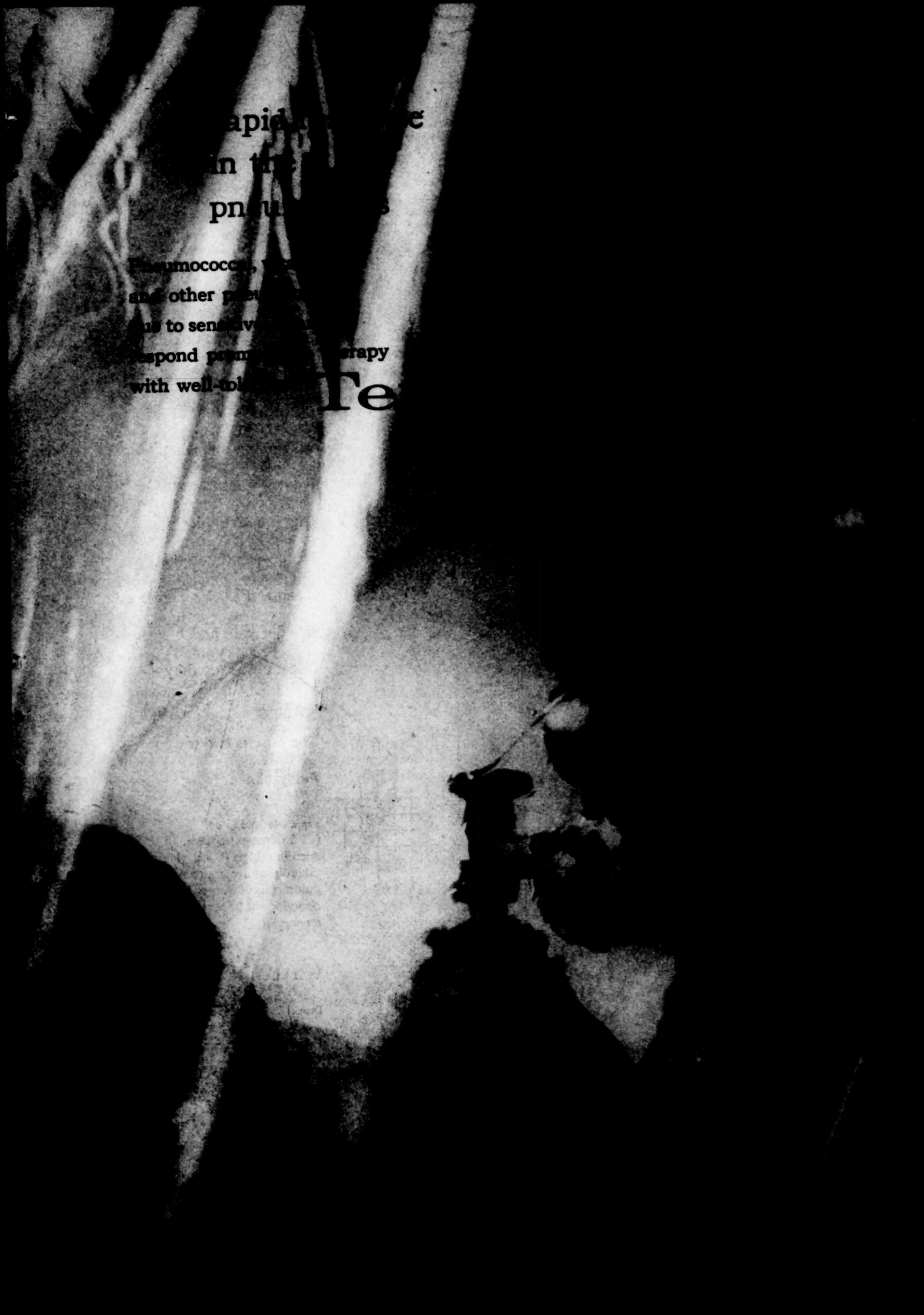
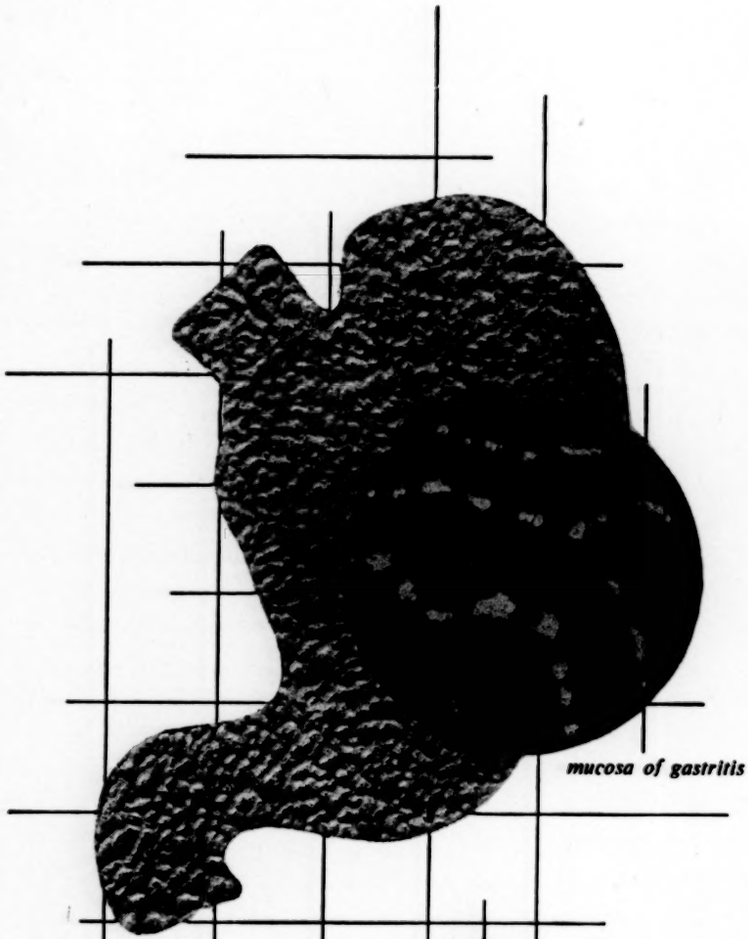


for

gastritis



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1. Rogers, M. P., and Gray, C. L.; *Am. J. Digest. Dis.*, 19:180. 1952.

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1. Quigley, T. B., and Renold, A. E.: New England J. Med. 246: 1012, 1952.

2. Steinberg, C. L., and Roodenburg, A. L.: J.A.M.A. 149: 1458, 1952.

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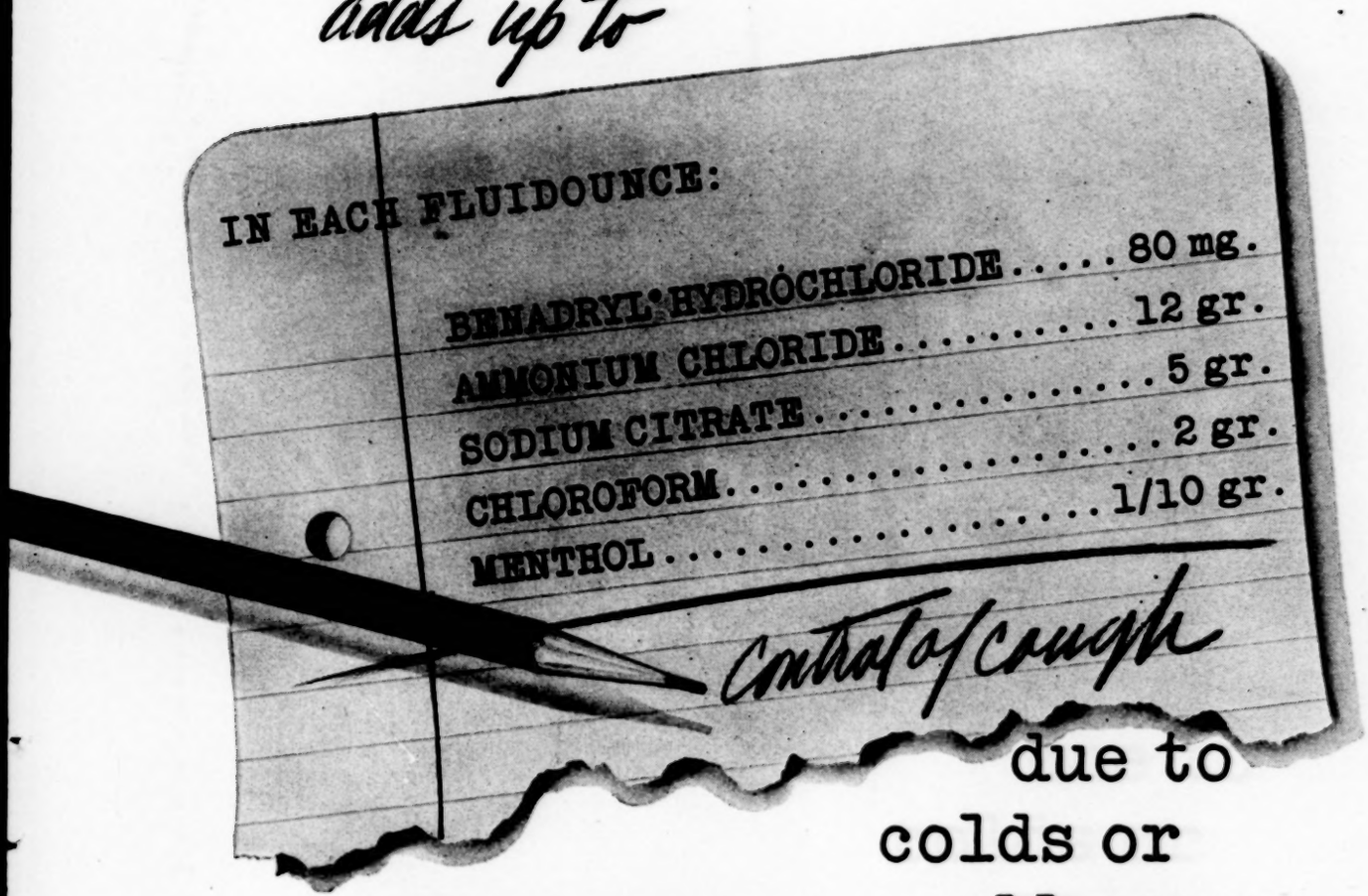

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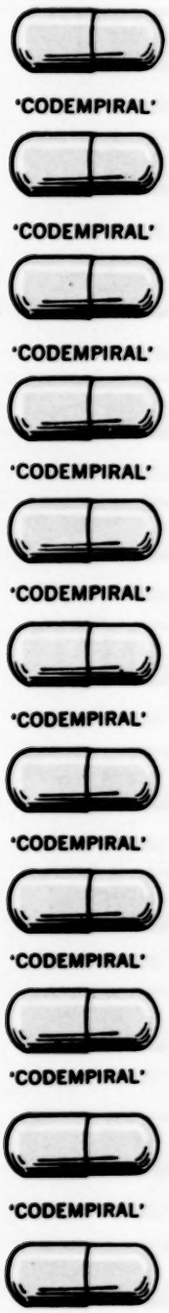

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Perloff, W. H.: Am. J. Obst. & Gynec. **58**:684 (Oct.) 1949.

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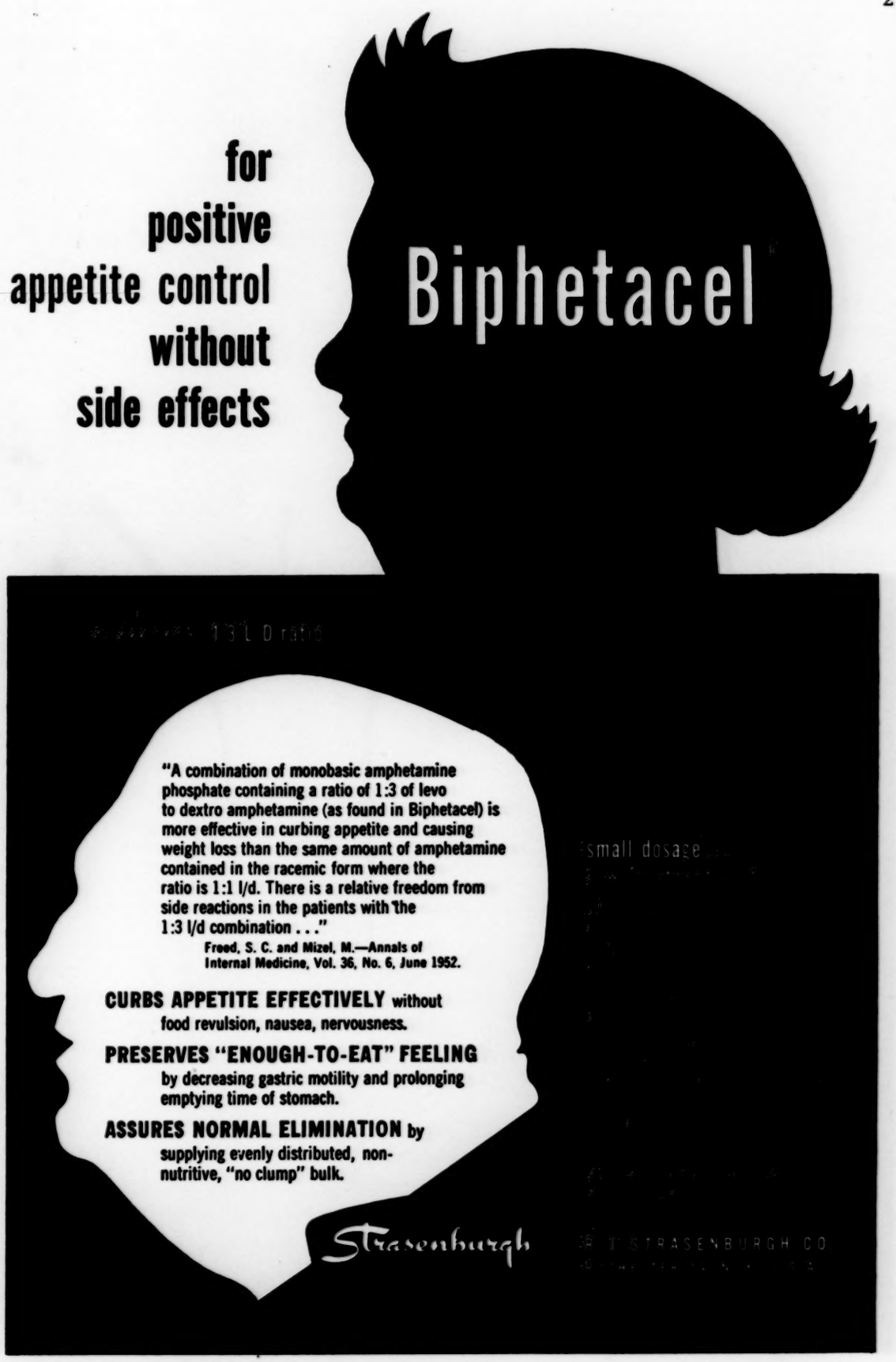
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Freed, S. C. and Mizel, M.—Annals of Internal Medicine, Vol. 36, No. 6, June 1952.
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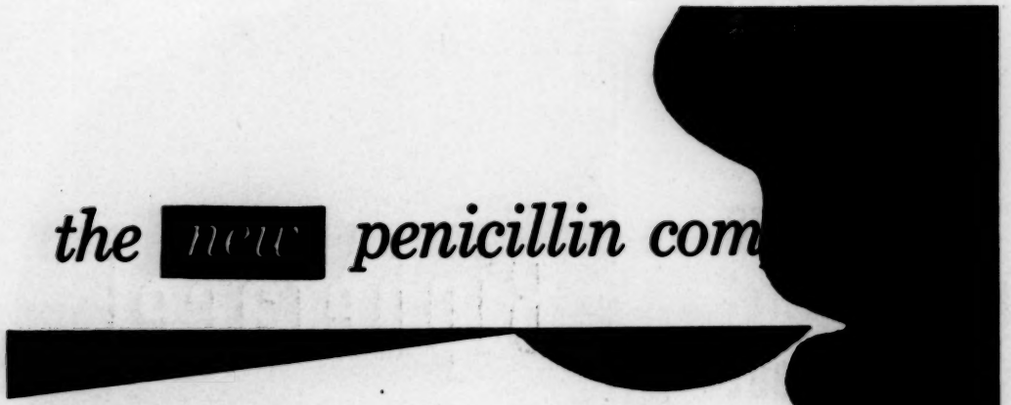

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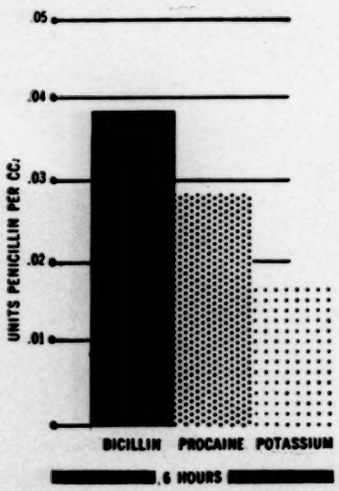

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**Smith, Richard T: Treatment of Neuritis with Protamide. New York Medicine {Aug. 20} 1952.*

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The American Journal of Medicine

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Editorial

Present Status of Atherosclerosis as a Derangement of Lipid Metabolism

THERE is accumulating indication that atherosclerosis is not necessarily an inevitable consequence of the intangible processes of aging, which one must accept with resignation, but may be due essentially to a derangement of lipid metabolism amenable to investigation and perhaps to prevention and cure. To be sure, mechanical factors play an important role in the causation of atherosclerosis: increased intra-arterial pressure; local turbulence in blood flow caused by irregularities and thickening of the intima or branching of vessels; and regional impairment of the elasticity of the vessel wall whether due to intrinsic disease of the media or to fixation of the vessel. Such mechanical factors appear usually, however, to be of secondary significance, largely in determining the sites where atherosclerotic plaques will deposit and in accelerating the rate of lipid deposition at these sites.

The underlying predisposition to atherosclerosis, the basic cause, appears more and more to be in the nature of a *metabolic defect* involving the biosynthesis, transport and catabolism or excretion of certain lipids, notably cholesterol in the form of lipoproteins. One indication of this is that atheromatous plaques are found on chemical analysis to contain a high proportion of cholesterol, in the form of cholesterol palmitate and other esters as well as some "free" cholesterol, together with significant quantities of cholesterol derivatives such as reduced cholesterol (dihydrocholesterol), oxidized cholesterol (cholestenone, which may be an artefact) and a carboxyl derivative of cholesterol as yet not fully identified. In addition, the plaques contain an appreciable concentration of phospholipids and a small percentage of neutral fat. Even if atheromas are not visible, chemical analysis of aortas has shown that the cholesterol content increases significantly and characteristically with age. Another reason why interest in arteriosclerosis has centered so largely on lipids and lipoproteins is the association of premature arteriosclerosis with diseases characterized by hypercholesteremia, such as familial xanthomatosis, familial hypercholesteremia, nephrosis and diabetes. Finally, there is the important fact that atherosclerosis can be produced experimentally in animals by the feeding of cholesterol. By overloading the capacity of the animal to metabolize or excrete the huge amounts of cholesterol fed, an error in lipid metabolism, so to speak, is induced. The lesions thus produced in the rabbit resemble only the earliest stage of the lesions found in man, the atheromatous plaque, but in the dog and chicken the full-blown picture of athero- and arteriosclerosis, similar in most essentials to that of man, can be reduplicated in the coronary, cerebral and other arteries.

Cholesterol, a steroid with an iso-octyl chain attached to carbon-17, occurs in the body largely esterified (in the carbon-3 position) with various fatty acids, chiefly unsaturated. Because of their non-polar characteristics, both esterified and free cholesterol do not circulate in the plasma in molecular solution but in more or less discrete combinations with certain plasma proteins, forming lipoproteins. This applies also to all or virtually all of the plasma phospholipids, chiefly lecithins, also sphingomyelins and cephalins; and, to a lesser degree, to the neutral fats. The lipoproteins so constituted can be separated by electrophoresis into α-lipoproteins and β-lipoproteins; by ethanol precipitation under controlled conditions into roughly corresponding fractions; by ultracentrifugation into a whole series of lipoprotein complexes of

varying cholesterol, phospholipid, neutral fat and protein content; and by paper electrophoresis.

Whereas until recently it was believed that the cholesterol of the plasma and tissues was derived largely if not entirely from ingested preformed cholesterol of the diet, as our information increases the cholesterol intake seems less and less important, at least in man and within the ordinary limits of dietary consumption. It is now known that most of the body cholesterol is synthesized at a lively rate from simple 2-carbon compounds, specifically acetate, which is in turn derived from fats, proteins and carbohydrates of the diet. It follows that elimination of preformed cholesterol from the diet is just a gesture, probably a futile gesture. It also follows that it is quite impossible, by dietary regulation, to block altogether the biosynthesis of cholesterol; nevertheless, restriction of caloric intake may decrease the magnitude of cholesterol biosynthesis and such restrictions seem prudent, according to present knowledge, even if their efficacy in prevention of atherosclerosis is as yet unestablished.

The bulk of the cholesterol formed in the body is elaborated in the liver but cholesterol is formed also in smaller quantities in many tissues, including the adrenal cortex, skin, intestinal wall, kidney, brain; and in the wall of the aorta, although at a low rate which may not be significant in relation to atherosclerosis. Just how the complex cholesterol molecule is synthesized in the body from 2-carbon acetate is not known. Recent experiments with C^{14}-labeled acetate by Bloch indicate that squalene, a long-chain unsaturated hydrocarbon composed of 6 isoprene units, is an intermediate, presumably with folding of the straight chain to form the ring compound. In any event the cholesterol so formed, whether synthesized or retained by hepatic or extrahepatic tissues, appears to be in equilibrium and for the most part freely miscible with the circulating cholesterol.

The ultimate fate of cholesterol in the body is still obscure. Of course, much cholesterol is excreted as such and in the reduced form of dihydrocholesterol and coprosterol through the gastrointestinal tract, by way of the biliary tract and more directly; also to some extent through other avenues of excretion. Some is converted to steroid hormones, steroid vitamins and bile acids. But from all indications these methods of disposal do not by any means account for the whole of the daily cholesterol turnover, the magnitude of which is indicated by an estimated eight-day half-life for cholesterol. It is highly probable that a significant proportion of the cholesterol store is degraded, although perhaps to a lesser extent in man than in such animals as the rat. The metabolic pathways involved are not known. Recently Chaikoff found that most of the C^{14} of cholesterol labeled in the iso-octyl side chain rapidly appeared in the carbon dioxide of the expired air; C^{14} incorporated into the ring structure was recovered in the *saponifiable* fraction of the fecal steroids. These saponifiable compounds have not yet been identified but presumably reflect drastic changes in composition. They may be related to the 27-carbon acid isolated by Cook from the feces of rats fed cholesterol.

There is no precise information available as yet as to what goes wrong, in atherosclerotic subjects, with the normal metabolic processes involving the formation and disposition of cholesterol. It may be presumed that cholesterol is deposited in the vessel walls and in other tissues when more is formed or absorbed than can be maintained in solution in the extracellular fluid and excreted or degraded. The possibilities now under active investigation include: 1. Biosynthesis of excessive amounts of cholesterol which cannot be metabolized or excreted sufficiently rapidly and hence tend to accumulate in tissues least able to cope with the excessive production or deposition. 2. Abnormalities in transport mechanisms or in transport compounds with impairment of the stability of cholesterol colloids in the plasma, thus favoring deposition in the arterial walls. 3. Interference with the transit of cholesterol and other lipids through the arterial wall or impairment of catabolic processes there. 4. Excessive absorption of cholesterol from the gastrointestinal tract or decreased excretion through the biliary or gastrointestinal tract. It is likely that more than one of these mechanisms is involved in the pathogenesis of atherosclerosis. It is already clear that different mechanisms play predominant roles under different circumstances.

There is a primary difficulty in all such investigation of atherosclerosis in the living human subject and that is the present impossibility of quantifying the number and size of arterial lesions, and of estimating directly the effectiveness of dietary or other measures which may decrease the amount of atherosclerosis. It is im-

possible to do a satisfactorily controlled experiment in man, with direct analysis of the effects on deposition of lipids in the arterial tree. One is dependent upon animal experiments, which may or may not be directly referable to man; or if working with man, upon tangential determinations of serum lipids or lipoproteins, which may or may not reflect corresponding lipid changes in the arterial walls; or upon evidences of impairment of blood flow in the coronary or cerebral vessels, which often do not faithfully reflect atherosclerotic vessel changes elsewhere; or upon x-ray indications of calcification of the vessel wall, certainly a late and unreliable criterion. Present information as to the role of metabolic factors in atherogenesis in man is therefore based largely upon indirect evidence of greater or lesser statistical probability.

There would seem nevertheless to be little doubt now that the occurrence of coronary thrombosis relatively early in life can be correlated in many instances with abnormally high and fluctuating serum cholesterol levels representing either an inborn error of lipid metabolism or associated with some disease affecting the lipid metabolism, such as diabetes. In such instances there is also apt to be a significant increase in the plasma cholesterol-phospholipid ratio, an increase in plasma Sf 12–20 and related lipoproteins, and a relative and absolute increase in the plasma β-lipoproteins at the expense of the α-lipoproteins. These probably are all different facets of the same basic lipid disturbance.

Granting this to be true there remains the question whether the high incidence of arteriosclerosis in the older population of this country also is ascribable basically to what must then be a very widespread metabolic derangement of lipid or lipoprotein metabolism, presumably of such low order as to become apparent ordinarily only late in life, and then particularly if aggravated by a general over-indulgence in food. There is some evidence for this view. In general, quite striking increase in serum lipids and lipoproteins occurs with age in apparently normal subjects. There is a significant increase in serum cholesterol after the age of forty in both males and females. Further, according to Gofman and associates, there is an increase in plasma Sf 12–20 lipoproteins from a median of 28 mg. per cent at age twenty-five to a median of 40 mg. per cent at age thirty in males, with a smaller but steadier accumulation in females whose median reaches 40 mg. per cent only between ages of fifty and sixty. And, according to Barr and associates, the plasma β-lipoproteins are, in general, lower in young women than in young men between the ages of eighteen and thirty-five but reach about the same, somewhat higher levels in both sexes between the ages of forty-five and sixty-five. It is possible to discern in these relationships the elements of a significant correlation with the clinical facts regarding the incidence of coronary thrombosis in various age groups and in the two sexes.

ALEXANDER B. GUTMAN, M.D.

Clinical Studies

Cardiac Catheterization in Interatrial Septal Defect*

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Los Angeles, California

THE purpose of this report is an evaluation of the findings obtained by cardiac catheterization in ten patients with proven interatrial septal defect. Similar series of patients have recently been reported in detail by Hickam,[1] Limon,[2] Barber[3] and Keith.[4]

Our interest has been particularly in the physiology of isolated interatrial septal defects, and in order to study this group adequately we have made an effort to exclude patients with associated lesions such as transposed pulmonary veins and pulmonary stenosis. The hemodynamic problems include: (1) direction and degree of shunt flow, (2) auricular pressures in relationship to direction of shunt, (3) causes of arterial unsaturation and (4) degree and nature of increased pulmonary vascular resistance.

In addition to the foregoing hemodynamic problems a fundamental consideration is the feasibility of surgery in atrial septal defect. Surgery as a definitive treatment of interatrial septal defect depends mainly on the concept that the defect is, in itself, the primary intracardiac lesion. If this is the case, a surgical procedure such as that of Murray[5] will be of great value. However, it has been our experience that not infrequently the catheterization has "uncovered" some other lesion of greater importance than the atrial septal defect, such as pulmonary stenosis or transposed pulmonary veins. These operable lesions may represent the primary cardiac defect for which the atrial septal defect is a compensatory shunt.

METHOD

Cardiac catheterization was performed according to the routine Cournand procedure.[6] Intracardiac pressures were recorded with strain gauge manometers and oscillographic amplification. Blood oxygen determinations were carried out by the Van Slyke technic and arterial samples drawn through inlying femoral, radial or brachial artery needles. Oxygen consumptions were obtained by using a wet test meter and Pauling analyzer.

CASE REPORTS

CASE I. G. M., a twenty-seven year old white woman, had no history of rheumatic fever, sore throat or scarlet fever as a child. In 1943, while in the Navy, the patient had an episode of epistaxis, arthralgia, fever and elevated sedimentation rate. A diagnosis of rheumatic fever was made and a heart murmur noted for the first time. In 1949 the patient was again hospitalized for rheumatic fever with complaints of nocturnal dyspnea, orthopnea, hemoptysis and ankle edema. On entry slight shortness of breath was the only complaint.

On physical examination the patient was a well developed, well nourished white woman. No cyanosis or clubbing was present. The blood pressure was 110/60. The apex was in the fifth interspace, 1 cm. outside the mid-clavicular line. The rate and rhythm were normal. There was accentuation of the mitral first sound and pulmonary second sound. A grade 2 pulmonary systolic murmur and grade 5 high pitched blowing pulmonary diastolic murmur were present. A third sound was present at the apex. The lungs were clear. There was no edema.

An electrocardiogram showed the pattern of right ventricular hypertrophy. Fluoroscopy showed the heart to be of normal size and shape.

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There was no isolated chamber enlargement and no unusual features of the pulmonary vascular shadows were noted. The hemoglobin was 15.3 gm.

CASE II. J. C., a fifty-two year old white man, had a vague history of intermittent cyanosis and dyspnea as a child. In World War I the discovery of a heart murmur resulted in a medical discharge from the service. There was a history of pneumonia on two occasions in 1926 and 1932. In 1932, 1933 and 1934 the patient was treated for pulmonary tuberculosis.

On physical examination the patient appeared well developed and well nourished, and without dyspnea, but there was mild cyanosis of the nail beds and lips. No clubbing was present. The blood pressure was 140/85. The rate and rhythm were normal. The cardiac apex was in the fifth interspace at the mid-clavicular line. There was slight accentuation of the pulmonary second sound. A grade 4 systolic murmur was present in the third and fourth left interspaces.

An electrocardiogram showed the pattern of incomplete right bundle branch block. Fluoroscopy of the chest showed mottling at both apices suggestive of old pulmonary tuberculosis. In the postero-anterior position there was straightening of the upper left cardiac border, with prominence in the region of the pulmonary artery, and a very small aortic knob. Right ventricular hypertrophy was noted in the left oblique position. The red count was 5.04 million, hemoglobin was 15.5 gm.

CASE III. P. D., a nineteen year old white woman, gave a history of shortness of breath "as long as she could remember." She was unable to take part in normal childhood and adolescent activities. There was no history of cyanosis, but a heart murmur had been known since infancy.

On physical examination the patient was slender but not stunted in growth. No cyanosis or clubbing was present. The blood pressure was 130/70; the rate was 85. Occasional premature beats were present. The apex impulse was in the fifth interspace in the mid-clavicular line. A diastolic thrill was present in the pulmonary area. Harsh systolic and diastolic murmurs were present in the pulmonary area. The systolic component was heard over the entire chest. The lungs were clear. There was no peripheral edema.

The electrocardiogram showed the pattern of right ventricular hypertrophy. X-rays of the chest showed 17 per cent enlargement by the Hodges-Eyster formula. There was a prominent pulmonary conus, and prominent arterial markings were present in the lung fields. The hemoglobin was 16 gm.

CASE IV. C. H., a nineteen year old white woman, was known to have had "heart trouble" since the age of eighteen months. She had been short of breath all her life on mild activity and had noted increasing coldness and cyanosis of the fingers during activity.

On physical examination the patient was thin but growth was not stunted. Slight cyanosis of the fingers, without clubbing, was present. The blood pressure was 110/70; the rate was 85 with occasional ventricular premature beats. The apex impulse was in the fifth interspace, 1 cm. to the left of the mid-clavicular line, but there was no enlargement to percussion. The pulmonary second sound was accentuated. A grade 3 pulmonary systolic murmur was present. The lungs were clear. There was no peripheral edema.

Electrocardiogram showed right ventricular hypertrophy. Fluoroscopy of the chest showed normal heart size. The pulmonary arc and pulmonary arteries were prominent. There was questionable "hilar dance." The hemoglobin was 13 gm.

CASE V. W. H., a seven year old boy, had a history of a "murmur" recognized shortly after birth. The child developed slowly and was mentally retarded. There was a questionable history of cyanosis on exercise. There was no restriction of activity and no history of shortness of breath.

On physical examination the boy was well developed and nourished. No cyanosis or clubbing was present. The blood pressure was 95/70; the rate and rhythm were normal. The pulmonary second sound was prominent. A harsh, grade 3 systolic murmur was heard in the pulmonary area, radiating to the neck, both axillas and back. No diastolic murmur was heard. The lungs were clear and no peripheral edema was present.

Electrocardiogram showed the pattern of right ventricular hypertrophy. On x-ray the heart was not enlarged. There was no marked enlargement of the pulmonary conus. The lung fields showed increased prominence of the vascular markings but there was no evidence of "hilar dance." The hemoglobin was 12.5 gm.

CASE VI. M. B., a twenty-two year old single,

white man, was found to have heart disease at the age of six months during treatment of pneumonia. There was a history of stunted growth until the age of eight but since that time growth had been normal. There was no history of cyanosis or clubbing. Since the age of twelve shortness of breath on exertion and limitation of activity had become more noticeable. During the past five years precordial pain and palpitation, precipitated by eating, had been present.

On examination the patient was well developed but underweight. No cyanosis or clubbing was present. The blood pressure was 110/70. The rate and rhythm were normal. The heart border was 2 cm. to the left of the mid-clavicular line. There was a very rough grade 4 systolic murmur in the pulmonary area, accompanied by a thrill and followed by a short diastolic murmur. Short grade 2 systolic murmurs were present at the apex and aortic areas. The lungs were clear. No edema was present.

Electrocardiogram showed the pattern of incomplete right bundle branch block. Fluoroscopy revealed a greatly enlarged main pulmonary artery and right ventricular hypertrophy in the left oblique position. The pulmonary vascular shadows were prominent. The hemoglobin was 16 gm.

Case VII. H. A., a thirty year old white housewife, had a history of slight shortness of breath on exertion for the past five years. Shortness of breath appeared after climbing eight or ten steps, or walking six or eight blocks. There was no history of cyanosis or clubbing.

On physical examination the patient was well developed and nourished. There was no cyanosis or clubbing. The blood pressure was 95/60. The apex impulse was in the fifth interspace, 1 cm. outside the mid-clavicular line. The rate and rhythm were normal. The pulmonary second sound was accentuated. A harsh systolic murmur with thrill and a high pitched early diastolic murmur were present in the pulmonary area. The lungs were clear. There was no peripheral edema.

Electrocardiogram showed the pattern of right ventricular hypertrophy. X-rays of the chest revealed a very prominent pulmonary conus. The pulmonary vascular markings were accentuated and "hilar dance" was present. The hemoglobin was 13 gm.

Case VIII. H. B., an eighteen year old single woman, gave a history of a heart murmur since birth. There was no history of cyanosis until the fifth year, following scarlet fever. Following this persistent cyanosis was present. Clubbing of the toes and fingers ensued. The patient had markedly limited her activity on the advice of physicians. During the eight months before admission she had a severe gastrointestinal hemorrhage and several splenic infarcts.

On physical examination the patient was underdeveloped and poorly nourished. There was moderate cyanosis and clubbing of the fingers and toes. The blood pressure was 110/70 in both arms. The apex impulse was in the fifth interspace within the mid-clavicular line. A second impulse was felt in the pulmonary area, and a systolic thrill was present at this area. The pulmonary second sound was accentuated. The rate was 90 and the rhythm regular. A grade 4 systolic murmur was present in the pulmonary area, transmitted toward the left axilla. No diastolic murmurs were present. The lungs were clear. The liver was felt below the right costal margin but no edema was present.

Electrocardiogram showed the pattern of incomplete right bundle branch block. X-rays of the heart showed some dextroposition of the heart, and the right leaf of the diaphragm was depressed. The lung fields and vascular markings were within the normal range. The hemoglobin was 17.5 gm.

Case IX. J. B., an eight year old white girl, was first informed at the age of five that she had a murmur that probably had been present since birth. There was no history of cyanosis or severe limitation of activity. Within the past year the patient became fatigued more than other children of her age. There was no history of rheumatic fever.

On physical examination the child was thin and poorly developed. A prominent bulge of the upper mid-chest was noted. The apex was in the fifth interspace at the anterior axillary line. A diastolic thrill and a prolonged rumbling diastolic murmur were present at the apex. P_2 was greater than A_2. The rate was 100 and regular. A coarse, grade 4 systolic murmur with thrill was present in the third and fourth left interspaces. The blood pressure was 110/70. The lungs were clear. No cyanosis, clubbing or edema were present.

The hemoglobin was 11 gm. Electrocardiogram showed right ventricular hypertrophy and first degree A-V block. The orthocardiogram revealed generalized cardiac enlargement, predominately of the right ventricle. There was no

selective enlargement of the left auricle. The pulmonary vascular markings were very prominent, but no "hilar dance" was seen.

CASE X. R. H., a thirty-eight year old white man with a history of bronchial asthma since the age of three, complained of shortness of breath of ten years' duration. He had had cyanosis of the hands and lips and swelling of the ankles for one year, and because of these symptoms he was placed on digitalis.

On physical examination on entry the patient was orthopneic, dyspneic and cyanotic, appearing acutely ill. Clubbing of the fingers and toes was present. Neck veins were distended. The blood pressure was 120/90. The apex impulse was 1 cm. outside the mid-clavicular line. The pulse was 100 and regular. Heart tones were of fair quality. The pulmonary second sound was accentuated. No murmurs were heard. Numerous inspiratory and expiratory wheezes were heard throughout both lung fields. The liver was felt two fingers below the right costal margin. No peripheral edema was present.

Electrocardiogram showed marked right ventricular hypertrophy with a pattern of incomplete right bundle branch block. X-ray examination of the heart showed generalized cardiac enlargement, right ventricular in type. The hemoglobin was 24 gm. (14 per cent). (In this patient the diagnosis of atrial septal defect was made at autopsy and not at the time cardiac catheterization was performed.)

At autopsy the heart weighed 740 gm. A 4 cm. defect was found in the area of the foramen ovale, which was completely fenestrated, the largest defect measuring 1.5 cm. in diameter. The right ventricular wall was up to 9 mm. in thickness, and the pulmonic and tricuspid valves measured 10 cm. and 13.5 cm., respectively. There was some atherosclerosis of the larger pulmonary arteries. Microscopic section of the lung showed marked hyalinization of small arterioles and chronic inflammatory reaction in the alveoli. The final diagnoses were bronchial asthma, emphysema, cor pulmonale and atrial septal defect.

SUMMARY OF CLINICAL CASES

The clinical features segregate these patients into two clinically recognizable groups depending on the direction of the shunt flow. These studies elucidate and amplify the findings noted in our previous series.[7] Shortness of breath was conspicuous and of long duration in all patients except W. H. A history of cyanosis was present in four patients. Heart failure was not reported except in the case of patient G. M.

On physical examination the heart was usually not enlarged. A pulmonary systolic murmur was a constant finding and a pulmonary diastolic murmur was heard in four of the nine cases recognized by catheter examination. The blood pressure appeared within the normal range. Cyanosis was present in the four patients previously mentioned. Of interest is the fact that none of the cyanotic patients had a palpable thrill over the pulmonic area. Four of the six patients without cyanosis had recognizable thrills in the pulmonic area. Also the roentgen findings in the cyanotic group showed absence of prominent pulmonary vascular shadows except in the case of C. H. In the acyanotic group five of the six patients had prominent vascular markings.

TABLE I
COMPARATIVE CLINICAL FEATURES IN ATRIAL SEPTAL DEFECTS

Clinical Features	Major Shunt Right to Left (4 cases)	Major Shunt Left to Right (4 cases) or Mixed (2 cases)
Age	2 over 35 yr.	None over 30 yr.
Cyanosis	Present in all 4	Absent in all 6
Pulmonic thrill	Present in none	Present in 4
X-ray prominence of the pulmonary vascular tree	Present in 1	Present in 5

The electrocardiogram showed evidence of right ventricular hypertrophy in every patient, with the pattern of incomplete right bundle branch block in four of the nine cases proved by catheterization. An unexpected finding was the marked variation of the QRS pattern in six, which appeared different in contour in each of the nine cases. Reference to Table I will show the important clinical features differentiating predominantly right to left from left to right shunts.

COMMENTS

Atrial septal defect can be positively identified only if the catheter passes through the defect. In our series the most definitive approach to this problem has been to show the catheter posi-

tioned in a left pulmonary vein, and then successively withdrawn into the left atrium and right atrium. Other findings in cardiac catheterization are not wholly diagnostic, as will be shown. Tables II and III reveal that in all cases but one the catheter entered the left auricle. In four cases the pulmonary vein was entered as well. In one patient, R. H., the diagnosis of atrial septal defect was not proven until autopsy.

In addition to the ten cases reported, seven patients were catheterized in whom the diagnosis of interatrial septal defect was "presumptive." Of this group five patients showed a rise of oxygen content of at least two volumes per cent from superior vena cava to right auricle. One patient had a borderline increase in oxygen content. In the final patient the pulmonary vein was entered but a superior vena cava oxygen content was not obtained.

These patients were considered "presumptive" examples of interatrial septal defect since their findings may be simulated exactly by partial transposition of the pulmonary veins into the right auricle. Although this anomaly is not common, we have met with five cases among 150 cardiac catheterizations and believe it is more frequent than realized. It has been our experience that unless a very definite effort is made to search the lateral wall of the right atrium with the tip of the catheter such a diagnosis will be easily missed. The patients in the "presumptive" group are not included in the tables or the subsequent discussion.

Predominant Left to Right Shunts. A typical left-right shunt in septal defect is substantiated by the following findings: In the pulmonary vein oxygen saturation approaching 96 per cent is the rule. In withdrawing the catheter tip to the left atrium there is a slight drop in saturation. On further withdrawal of the catheter to the right atrium a marked drop in oxygen content and saturation occurs, produced by the admixture of blood entering the right atrium from the superior and inferior vena cava, and from the coronary sinus. In comparing the oxygen content of the right atrium with that of the superior and inferior vena cava a definite rise of 1.5 to 2.0 volumes per cent is noted.[8] This rise of oxygen content from venous system to right atrium is usually evident but may be masked if a representative sample from the right atrium is not selected. In other words, if a single sample is chosen in which the catheter tip lies near the opening of the coronary sinus such a "right auricular" sample may show no rise whatever, but even a fall in oxygen content may be noted.

In addition to securing a "representative" sample from the right atrium Limon[2] has emphasized the importance of securing a "representative" sample from the cavae. By rotating the catheter tip in the inferior vena cava Limon

TABLE II

PRESSURE STUDIES IN ATRIAL SEPTAL DEFECTS

Name	Sex, Age	Superior Vena Cava			Right Auricle			Left Auricle			Pulmonary Vein			Right Ventricle			Pulmonary Artery			Peripheral Artery		Shunt
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	
G. M.	F, 27	..	..	1.5	..	..	1.5	..	..	3.5	..	..	..	...	..	34	...	..	59	...	..	Left–right
J. C...	M, 52	..	..	7	..	..	7	..	..	6	..	..	..	...	..	10	...	..	14	125	60	Right–left
P. D..	F, 19	5	−1	...	5	−1	...	5	−1	...	6	−2	..	...	..	30	...	..	65	...	..	Mixed
C. H.	F, 19	15	5	...	15	5	...	15	0	...	..	..	..	...	..	..	...	..	..	...	..	Right–left
H. B..	F, 18	..	..	...	11	9	...	13	11	...	18	15	..	...	..	..	...	..	..	106	60	Right–left
W. H.	M, 7	..	..	1.5	..	..	1.5	..	..	1.8	..	..	..	...	..	..	...	..	..	...	..	Mixed
M. B.	M, 22	5	0	...	6	1	...	8	1	...	..	..	..	123	8	..	123	60	..	130	70	Left–right
H. A.	F, 30	3	0	...	3	0	...	10	1	...	..	..	..	70	0	..	70	25	..	...	..	Left–right
J. B...	F, 8	7	5	...	7	3	...	9	5	...	15	11	..	45	0	..	45	20	..	...	..	Left–right
R. H.*	M, 38	15	6	...	15	6	...	..	..	...	..	..	..	80	10	..	75	40	..	...	..	Right–left

* Proven by autopsy but not by cardiac catheterization

has come to the conclusion that marked differences—as much as 3 to 4 volumes per cent—may exist in the inferior vena cava itself, and that laminar flow is present. In other words there is incomplete mixing of various return flows from kidney, lower extremities and liver, with the flow from each organ maintaining its "own" oxygen content. Brannon et al.[9] and Banghart[10] believe that "mixed" superior and inferior vena cava blood constitutes a more "representative" sample than that of either vena cava alone.

Four of our ten patients in Tables II and III (M.B., H.A., G.M. and J.B.) appear to have had predominantly left to right shunts. Thus three of these had a relatively normal arterial oxygen saturation; in the other, although no peripheral artery sample was obtained, the oxygen saturations of pulmonary vein and left atrium were approximately equal. The oxygen increments in right atrium compared to superior vena cava were 3.8, 4.0, 3.1 and 2.9 volumes per cent, respectively.

Predominant Right to Left Shunt. Occasional patients with atrial septal defect may show a predominant or total right to left shunt. This situation is often produced in the presence of an additional lesion involving the right side of the heart, such as primary pulmonary disease, pulmonary stenosis or mitral stenosis with borderline or frank right-sided heart failure.

The catheterization findings in this situation are strikingly different from those in left to right shunts. In addition it is important to emphasize that when a predominantly right to left shunt is present with atrial septal defect, the diagnosis may be missed entirely when the catheter does not enter the left atrium and pulmonary vein.

TABLE III

BLOOD OXYGEN STUDIES IN INTERATRIAL SEPTAL DEFECT

Name	Sex Age	Oxygen Content							Oxygen Saturation			O_2 Capacity	Shunt
		Superior Vena Cava	Right Auricle	Left Auricle	Pulmonary Vein	Right Ventricle	Pulmonary Artery	Peripheral Artery	Pulmonary Vein	Left Auricle	Peripheral Artery	Vol. % O_2	
G. M.	F, 27	11.60	15.40	18.25	18.55	14.25	14.45	.....	89.3	87.9	.....	20.70	Left–right
J. C...	M, 52	11.80	12.42	17.66	.....	12.33	.....	17.88	.....	85.0	86.1	20.78	Right–left
P. D..	F, 19	12.40	15.45	16.27	18.13	.....	.....	15.87	90.76	81.5	79.4	19.97	Mixed
C. H..	F, 19	10.59	11.3	16.45	.....	.....	.....	14.12	.....	93.41	80.2	17.61	Right–left
H. B..	F, 18	.....	15.81	20.07	23.47	.....	.....	19.06	97.6	83.5	79.3	24.05	Right–left
W. H.	M, 7	10.98	11.12	14.65	.....	.....	.....	.....	.....	92.2	.....	15.89	Mixed
M. B..	M, 22	12.47	16.48	20.47	.....	18.20	18.02	19.76	.....	94.03	90.77	21.77	Left–right
H. A..	F, 30	12.27	15.35	17.96	.....	15.53	15.33	17.47	.....	96.3	93.6	18.65	Left–right
J. B...	F, 8	9.81	12.71	13.49	.....	12.60	12.96	13.33	.....	89.75	86.57	.....	Left–right
R. H.*	M, 38	8.04	7.35	.....	.....	9.56	9.35	15.53	.....	.....	65.3	23.8	Right–left

* Proven by autopsy but not by cardiac catheterization

The oxygen saturation in the pulmonary vein is the same as in left to right shunts and approaches 96 per cent in the absence of pulmonary disease. When the catheter is withdrawn to the left atrium, a marked drop in saturation results as the catheter is introduced into the stream of blood coming through the defect from the right.[2] As the catheter is withdrawn further a lesser drop in saturation occurs, depending, of course, on the size of the shunt itself. In this situation there should be little or no difference in oxygen content between mixed caval blood and that in the right atrium, since little or no left atrial blood enters the right atrium. It is obvious that if the catheter does not enter the left atrium, the diagnosis of atrial septal defect will be missed in the presence of a predominant right to left shunt.

Four of our patients showed predominant right to left shunts, R. H., H. B., J. C. and C. H. The first patient had primary cor pulmonale and the atrial septal defect was not diagnosed at the time cardiac catheterization was performed, but at autopsy. These present excellent illustrations of the difficulties of catheterization diag-

nosis of atrial septal defect in the presence of a predominant right to left shunt. The maximum rise in oxygen content between the superior vena cava and the right atrium was 0.7 volumes per cent. We believe this to be quite important. It shows how easily errors of diagnosis might arise during catheterization. Such small differences would never have disclosed the presence of an atrial septal defect. Again the passage of the catheter through the defect itself must be emphasized as the sole positive criterion of diagnosis.

In this connection the data of Limon[2] on mixed shunts appear important. In eight of his cases the *mean* rise of oxygen content between right atrium and superior vena cava was only 1.5 volumes per cent. In one of our cases (R. H.) there was a drop of 0.6 volumes per cent between cava and atrium. Here, the ventricular sample showed a rise of 1.5 volumes per cent over the caval saturation and was erroneously reported as evidence of a ventricular septal defect. A small left to right shunt was undoubtedly present but the right atrial sample was most likely drawn from a location near the opening of the coronary sinus. The evidence for a primary right to left shunt is in this case indirect, since no left auricular or pulmonary vein sample was obtained. However, because of the elevated right atrial pressure (the patient was in mild right-sided failure during cardiac catheterization) it is presumed that a predominant right to left shunt was present as an important additional factor in the production of the gross arterial desaturation.

The remaining three cases showed desaturation in the left atrium of a more marked degree than the four predominantly left to right shunt patients. In one, H. B., the pulmonary vein was entered and 97 per cent oxygen saturation was found as compared to 84 per cent in the left atrium, demonstrating that cyanosis was due to the shunt and not to pulmonary factors.

Bi-directional Shunts. In general most patients with atrial septal defect show "mixed" shunts. Usually the left to right shunt predominates, particularly in the younger patients. The truly bi-directional shunt reflects the interplay of the right to left and left to right flows through the septal defect without conclusive predominance of either flow. As in the shunts with major left to right flow there is oxygenation of the right atrium; in the shunts with major right to left flow there is desaturation of the left atrium. The femoral artery saturation is borderline, representing the admixture of right and left flows within the left atrium. Two of our cases fell into a bi-directional pattern. In one, P. D., the left to right flow evidence provided by a 3.1 volume per cent rise in oxygen saturation between superior vena cava and right atrium was balanced by a 2 volumes per cent drop from pulmonary vein to left atrium. Here, too, the peripheral artery was only 79 per cent saturated. In the other patient, W. H., the rise from superior vena cava to right atrium was but 0.1 volume per cent. The left atrium, however, showed 92 per cent saturation.

Atrial Pressures. Pressure contours in the right auricle have been well described by Bloomfield et al.:[11] "Auricular systole appears as a monophasic positive wave with its onset slightly after the P wave of the electrocardiogram. Associated with the onset of ventricular contraction is a small initial pressure rise, followed by a sharp fall. The initial rise, not present in all tracings, has been ascribed by Wiggers to the impact of the closing of the AV valves on the intra-auricular blood mass, or possibly to the slight regurgitation before closure. The pressure fall is attributed to the descent of the base of the heart during ventricular ejection. During the remainder of ventricular systole, the interauricular pressure gradually rises until the AV valves re-open. At this moment the pressure falls fairly abruptly as the auricle and ventricle become a common chamber, after which it gradually rises until the next auricular systole."

Pulse contours in atrial septal defect are usually higher in the left than in the right atrium.[12] Cournand[13] described the left atrial pressure as follows: "They differ greatly from blood pressure curves of the right auricle in the following characteristics: *A.* The pressure rise during the auricular systole was greater. In two cases where the tracings could be satisfactorily compared, the pressure at the peak of the auricular systolic wave in the left auricle averaged 13.1 mm. Hg as against 4.7 mm. Hg in the right. *B.* The slightly positive wave or notch corresponding to the onset of ventricular systole, clearly visible after the right auricular systolic wave, was *not* visible in the left auricular tracing." In three cases Cournand has averaged mean pulmonary vein, left auricular and right auricular pressures, viz., pulmonary vein 6.2, left auricle 4.1 and right auricle 1.4.

Our left auricular pressure curves in left to

right shunts have shown a higher mean pressure than that in the right auricle, usually 2 or 3 mm. Hg higher, and the individual pressure waves appear several times the size of their comparable right auricular equivalents. (Table II.) Little[14] has attempted to explain this increased left auricular pressure on the basis of diminished distensibility of the left auricle.

Pulmonary venous pressure curves have, in our experience, been particularly striking in showing (1) more well defined respiratory variations than auricular pressure curves and (2) less well defined individual waves.

Auricular pressure curves have been described in some detail in order to estimate their importance in determining the direction of the interatrial shunt. In the series of Calazel et al.[15] right atrial pressure was greater than left atrial pressure when a right to left shunt was present and opposite pressure changes were recorded in a left to right shunt. They found a small pressure differential in the presence of mixed shunts and believed that they could demonstrate reversal of pressure relationships during a portion of the cardiac cycle comparable to the shift in the direction of the shunt.

Our own small series of atrial pressure tracings supports the aforementioned conclusions. Mean pressure gradients between right and left atria in left to right shunts were −1, −2, −2 and −3 mm. Hg, respectively, in comparison to 1, 2 and 3.5 mm. Hg in right to left shunts. In the two mixed shunts without preponderance in either direction pressures were equal in the two atria.

Causes of Cyanosis. Arterial desaturation in atrial septal defects may be due to any of three factors. Normally there is some desaturation of arterial blood from the normal coronary venous channels entering the left atrium and ventricle. A second factor is the presence of a right to left interatrial shunt. A third possible factor is the presence of desaturation in the pulmonary venous blood. In addition to these three "arterial" causes of cyanosis there is the possibility of acrocyanosis in atrial septal defect as a fourth factor.

In general, from the series of Handelsman et al.,[16] Bing[17] and Hickam[1] it is apparent that pulmonary venous blood shows little desaturation except in the very unusual case. Our series, and that of Hickam, appears to show that the major degree of desaturation occurs in the left auricle and is due to a right to left shunt. An additional 3 to 4 per cent desaturation is produced by the entrance of normal coronary venous channels into the left ventricular cavity. Thus, given, let us say, an average oxygen saturation in the peripheral artery of 85 per cent in a typical atrial septal defect, practically all of this desaturation is due to the shunt itself. The amount of additional cyanosis produced peripherally (acrocyanosis) is speculative. Taussig[18] states that acrocyanosis due to increased oxygen utilization in the periphery "may" be present. We have no data on this point. It seems unlikely, however, that any additional reason is necessary for cyanosis since observable cyanosis is said to be apparent at about a level of 85 per cent arterial saturation.

In occasional cases of atrial septal defect marked cyanosis and clubbing are significant features. Selzer[19] in reviewing the literature has collected eleven such cases, 7 per cent of a total of 180 proven autopsy cases. Although it has been occasionally stated that complete reversal of flow with a total right to left shunt is a terminal complication of interatrial septal defect, this point of view is not substantiated by Selzer. All of his patients showed cyanosis for a period of two to thirty-five years. They appeared pathologically not to differ from the noncyanotic group. Pulmonary vascular changes were insufficient to account for the presence of cyanosis and Selzer concluded that free admixture of blood through large defects was the chief factor responsible.

The final dynamic problem in atrial septal defect concerns the pressure flow relationships in the pulmonary circulation. The pulmonary artery pressure in atrial septal defect varies widely. Barber[3] noted no rise of pulmonary artery pressure in twenty-one patients. In the group reported by Taylor et al.[20] all but one of nine patients had pressures over 30 mm. Hg systolic, but in general they were only moderately elevated. In our group we found moderate to marked elevation of pressure in six of seven patients. Such pressure levels correspond well with those of Healey[21,22] (moderate to marked elevation in four patients) and Hickam[1] (moderate to marked hypertension in three of four patients).

In view of the marked variations in pulmonary artery pressures, as noted previously, it is not surprising that calculations of pulmonary vascular resistance in atrial septal defect showed similar wide fluctuations. In general, our own

data show moderate increase in vascular resistance. However, as noted by Dexter[8] and others, tremendous flows may be present in the pulmonary circulation with no rise whatever in pressure, demonstrating greatly reduced resistance. The cause for increased vascular resistance in some patients with atrial septal defects remains obscure. Whether it results from the prolonged effect of increased right ventricular output (along with concomitant arteriolar changes) or whether it is a secondary result of anoxia caused by arterial desaturation remains to be seen. Welch[23] and Massee[24] have shown that arteriolar changes develop in patients with large pulmonary blood flow, and Motley[25] has recently related acute anoxia (though not chronic) to increased pulmonary artery pressure.

Our data illustrate two distinct types of patient with atrial septal defect. The younger patients without a history of cyanosis were shown to have high arterial oxygen saturations, high left atrial pressures, a marked rise of oxygen content between cavae and right atrium, full pulmonary vascular shadows and, frequently, a systolic pulmonic thrill. The older patients and those with other defects or heart failure had a history of cyanosis, low arterial oxygen saturation, elevated right atrial pressures, little or no rise of oxygen content between superior vena cava and right atrium, less prominent pulmonary vascular shadows and absence of a pulmonic thrill. (Table I.)

SUMMARY

1. Ten proven and seven presumptive cases with atrial septal defects have been presented.

2. The importance of catheterization of the left auricle is emphasized, together with the differential diagnosis of atrial septal defect from transposed pulmonary veins.

3. A rise of oxygen content in the right atrium in comparison to the oxygen content of the superior vena cava is not necessarily present in proven atrial septal defects.

4. The cause for cyanosis in atrial septal defect lies primarily in the presence of a right to left shunt.

5. The direction of shunt is determined by the pressure gradient between the atria during the cardiac cycle.

6. Pulmonary vascular disease may contribute to the pulmonary resistance but is not a significant factor in the production of cyanosis.

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REFERENCES

1. Hickam, J. B. Atrial septal defect. A study of intracardiac shunts, ventricular outputs and pulmonary pressure gradients. *Am. Heart J.* 38: 801, 1949.
2. Limon, L. R. and Rubio, A. I. Diagnosis of interauricular septal defects by catheterization. *Arch. Inst. Cardiol. México*, 19: 545, 1949.
3. Barber, J. M., Magidson, O. and Wood, P. Atrial septal defect with reference to the electrocardiogram, pulmonary artery pressure and second heart sound. *Brit. Heart J.* 12: 277, 1950.
4. Keith, J. D. and Forsyth, C. C. Auricular septal defects in children. *J. Pediat.*, 38: 172, 1951.
5. Murray, G. Closure of defects in cardiac septa. *Ann. Surg.*, 128: 992, 1948.
6. Cournand, A., Baldwin, J. S. and Himmelstein, A. Cardiac Catheterization in Congenital Heart Disease. New York, 1949. Commonwealth Fund.
7. Cosby, R. S. and Griffith, G. C. Interatrial septal defect. *Am. Heart J.*, 38: 80, 1949.
8. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sosman, M. C. and Evans, J. M. Studies of congenital heart disease. III. Venous catheterization as diagnostic aid in patent ductus arteriosus, tetralogy of Fallot, ventricular septal defect and atrial septal defect. *J. Clin. Investigation*, 26: 561, 1947.
9. Brannon, E. S., Weems, H. S. and Warren, J. V. Atrial septal defect. *Am. J. M. Sc.*, 210: 480, 1945.
10. Banghart, A. W. and Lewis, J. A. Intracardiac catheterization in interauricular septal defects. *Canad. M. A. J.*, 58: 605, 1948.
11. Bloomfield, R. A., Lauson, H. D., Cournand, A., Breed, E. and Richards, D. W., Jr. Recording of right heart pressures in normal subjects and in patients with chronic pulmonary disease and various types of cardio-circulatory disease. *J. Clin. Investigation*, 25: 639, 1946.
12. Lequime, J., Denolin, H., Gospel, F., Jonnart, L. and Wybauw, M. La communication interauriculaire, Etude clinique et physiopathologique de quatre cas. *Acta cardiol.*, 5: 312, 1950.
13. Cournand, A., Motley, A., Himmelstein, A., Dresdale, D. and Baldwin, J. S. Recording of blood pressure from the left auricle and pulmonary vein in human subjects with interauricular septal defects. *Am. J. Physiol.*, 150: 267, 1947.
14. Little, R. C., Opdyke, D. F., Haeley, J. G. Dynamics of experimental atrial septal defects. *Am. J. Physiol.*, 158: 241, 1949.
15. Calazel, P., Gerard, R., Daley, R., Draper, A., Foster, J. and Bing, R. J. Physiological studies in congenital heart disease. XI. A comparison of the right and left auricular, pulmonary capillary, and pulmonary artery pressures in nine patients with auricular septal defect. *Bull. Johns Hopkins Hosp.*, 88: 20, 1951.
16. Handelsman, J. C., Bing, R. J., Campbell, J. A. and Griswold, H. E. Physiological studies in con-

genital heart disease. V. Circulation in patients with isolated septal defects. *Bull. Johns Hopkins Hosp.*, 82: 615, 1948.

17. Bing, R. J. The physiology of congenital heart disease. *Nelson's Loose Leaf Med.*, 1950.
18. Taussig, H. B. Congenital Malformations of the Heart. New York, 1947. Commonwealth Fund.
19. Selzer, A. and Lewis, A. E. Occurrence of chronic cyanosis in cases of atrial septal defect. *Am. J. M. Sc.*, 218: 516, 1949.
20. Taylor, B. E., Geraci, J. E., Pollack, A. A. Burchell, H. B. and Wood, E. H. Interatrial mixing of blood and pulmonary circulatory dynamics in atrial septal defect. *Proc. Staff Meet., Mayo Clin.*, 23: 500, 1948.
21. Healey, R. F., Dow, J. W., Sosman, M. C. and Dexter, L. The relationship of the roentgenographic appearance of the pulmonary artery to pulmonary hemodynamics. *Am. J. Roentgenol.*, 62: 777, 1949.
22. Healey, R. F., Dow, J. W., Sosman, M. C. and Dexter, L. Roentgenographic appearance of interatrial septal defect. *Am. J. Roentgenol.*, 63: 646, 1950.
23. Welch, K. J. and Kinney, T. D. Effect of patent ductus arteriosus and interatrial and interventricular septal defect on the development of pulmonary vascular lesions. *Am. J. Path.*, 24: 729, 1948.
24. Massee, J. C. Atrial septal defect; correlation of necropsy with data obtained by right heart catheterization. *Am. J. M. Sc.*, 214: 248, 1947.
25. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A. and Dresdale, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.*, 105: 315, 1947.

Precipitation by Pulmonary Infection of Acute Anoxia, Cardiac Failure and Respiratory Acidosis in Chronic Pulmonary Disease

Pathogenesis and Treatment

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THE occurrence of acute fatal anoxia in chronic pulmonary disease is well recognized. Unfortunately the pathogenesis of this clinical picture and the role of infection are not always clearly understood. Furthermore, a lack of appreciation of the disturbed physiologic state often results in unsound or, at best, inadequate therapy. In the past few years the danger of oxygen therapy in the management of acutely ill patients who have underlying pulmonary disease has been stressed. The mechanisms leading to carbon dioxide retention and respiratory acidosis have been previously elucidated and modes of therapy, including artificial respiration, have been successfully applied.[1]

We have been impressed with a group of patients presenting the picture of chronic pulmonary insufficiency, with superimposed bronchial infection, acute anoxia and cardiac failure. The tendency to regard these patients simply as cases of cardiac failure or pulmonary infarction served as a stimulus to investigate them in order to elucidate the pathogenesis of the acute anoxia and a physiologic basis for therapy.

The purpose of this paper is to present several cases of chronic pulmonary disease illustrating the effect of infection and bronchial obstruction in producing acute anoxia; to show by physiologic studies the danger of oxygen therapy without some form of artificial respiration; and, finally, to present a therapeutic outline which has as its objectives relief of anoxia, control of infection and avoidance of decompensated respiratory acidosis.

MATERIAL AND METHODS

The patients studied had underlying chronic pulmonary disease with some degree of pulmonary insufficiency and initially were acutely anoxic. During the period of acute illness arterial punctures were performed and on each blood sample the following determinations were simultaneously made: (1) carbon dioxide and oxygen contents, oxygen capacity and saturation by the method of Van Slyke and Neill,[2] (2) partial pressures of carbon dioxide (pCO_2) and oxygen (pO_2) by the method of Riley et al.[3] and (3) in one case direct determinations of the pH utilizing the Cambridge Research pH meter.

Following clinical recovery, when possible, complete pulmonary function studies were performed, using the technics outlined by Baldwin et al.[4] for lung volumes, exercise responses, ventilation and blood gases. The analyses of gas tensions and calculation of alveolar-arterial oxygen gradients on room air, high and low oxygen mixtures, were performed by the technics

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outlined by Lilienthal and Riley.[5] Analysis of expired air for carbon dioxide and oxygen was performed on the micro-Scholander apparatus.

In two cases in which artificial respiration was used control studies were made to determine the effect of artificial respiration with and without oxygen therapy.

TABLE I

ARTERIAL GAS STUDIES IN CASE I

Date		CO_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pH calc.
11/27/50	Admission to hospital	51.3	18.0	56.3	38	71	7.19
1/8/51	Following recovery from infection	55.5	17.0	89.4	76	53	7.36

Analysis of all blood gases was done immediately upon withdrawal of a specimen. Duplicate determinations were performed on each specimen and the following checks were obtained: CO_2 content 0.2 volumes per cent; O_2 saturation 0.4 per cent; CO_2 and O_2 tensions 2 mm. of mercury; and pH 0.01 pH units. In our laboratory we have found a close correlation between the direct pCO_2 determination by the bubble technic and the calculated pCO_2 based on the Henderson-Hasselbalch equation, utilizing the direct pH measurement and the plasma CO_2 content.[6]

The pneumatic balance resuscitator (PBR) used in Case IV was a Burns model. A positive pressure equivalent to 15 cm. of water was obtained. The respirator used in Cases II, III and IV was of the Drinker-Collins variety. The pressures obtained were −15 during inspiration and +15 with expiration; the rate was 18 to 20 cycles per minute.

CASE REPORTS

CASE I. A forty-seven year old white male, railroad handyman was admitted on December 27, 1950, with weakness, cough and chest pain of four days' duration. The patient had been well until five months prior to admission at which time exertional dyspnea developed. Shortly before admission he developed a nonproductive cough, pleuritic type chest pain and cyanosis which progressed.

Physical examination on admission revealed a deeply cyanotic, obese white male with a temperature of 98°F., pulse of 100 and respiratory rate of 34 per minute. There was a frequent shallow cough productive of frothy, white sputum. The neck veins were distended. Examination of the chest revealed an increase in the anteroposterior diameter, diminished resonance to percussion and diminished intensity of the breath sounds throughout both lung fields and fine crackling rales at both bases. There was a sinus tachycardia of 100 and blood pressure was 102/80. The second pulmonic sound was accentuated. A firm, non-tender liver edge was palpated four fingerbreadths below the right costal margin. There was pallor and cyanosis of the extremities.

A hemogram was normal. There was 1 to 3 plus albuminuria, and occasional granular casts in the urinary sediment. Chest roentgenogram disclosed marked enlargement of the heart, mainly of the right side, prominence of the pulmonary artery and conus, a small right pleural effusion and congestive changes at both lung bases. The electrocardiogram revealed evidence of right ventricular strain. Arterial blood gas studies were performed. (Table I.) Blood urea nitrogen was 96 mg. per cent. Venous pressure was 256 mm. of water, decholin circulation time 22 seconds and ether time 9 seconds.

On the day of admission the patient was placed in an oxygen tent and given penicillin. He was digitalized rapidly with lanatoside C® intravenously and then maintained on digoxin. Despite these measures he remained markedly cyanotic and became less alert while in the oxygen tent. He remained afebrile but developed herpetic lesions about the mouth. On the fourth hospital day aureomycin was added to the therapeutic regimen because the patient was thought to have a virus pneumonia.

Because of the persistence of cyanosis and the patient's failure to respond to the usual measures for treatment of cardiac failure, a diagnosis of

pulmonary embolism was suggested and anticoagulant therapy was begun. Through the next weeks there was a slow progressive improvement with a rise in the blood pressure, diminution of the blood urea nitrogen, and clearing of congestive heart failure. The patient became more alert after removal from the oxygen tent several hours each day. Roentgenograms revealed decrease in the heart size and diminution of the pulmonary congestion. Arterial blood studies on January 8, 1951, demonstrated an increase in the pO_2, oxygen saturation and pH, and decrease in the pCO_2. (Table I.) Pulmonary function studies performed when the patient was asymptomatic revealed a typical pattern of pulmonary emphysema. (Tables I and V.)

TABLE II

ARTERIAL GAS STUDIES IN CASE II BEFORE, DURING AND FOLLOWING RESPIRATOR THERAPY

		CO_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pH calc.
7/2/51	Breathing room air	73.9	20.4	64.7	31	84	7.30
7/3/51	(a) Breathing room air, in respirator	72.6	21.0	69.1	35	75	7.34
	(b) Breathing oxygen, in respirator	75.0	20.8	82.3	61	75	7.36
	(c) Breathing oxygen, out of respirator	75.7	21.4	85.9	78	87	7.29
7/6/51	(a) After 3 days in respirator, breathing O_2	67.5	17.7	92.8	82	72	7.32
	(b) Breathing room air, out of respirator	66.7	17.7	81.3	56	71	7.32
8/3/51	Following recovery:						
	(a) Breathing room air	53.9	19.6	88.9	69	57	7.33
	(b) Breathing 29% oxygen	57.5	19.6	95.3	99	62	7.33

CASE II. A sixty-two year old white male printer was admitted on June 30, 1951, with dyspnea, orthopnea and cough of two weeks' duration. The patient had a history of pneumonia in childhood and recurrent pulmonary infections since the age of eighteen. He noted frequent productive cough, wheezing and dyspnea. Two weeks prior to admission the symptoms became progressively more severe and pedal edema was noted for the first time.

At the time of admission the patient appeared chronically ill, cyanotic and tachypneic. The temperature was 100°F., the pulse was 96 and regular, the blood pressure 160/70. Mucoid secretion was noted in the pharynx. There was an increase in the anteroposterior diameter of the chest, generalized wheezing throughout both lung fields and moist rales at both lung bases. Cardiac examination was normal except for an accentuated second pulmonic sound. The liver was palpable two fingerbreadths below the right costal margin and there was moderate ankle and sacral edema.

A roentgenogram of the chest revealed extensive emphysema and fibrosis. An electrocardiogram was consistent with right ventricular hypertrophy. Blood count revealed 5.4 million red blood cells, hemoglobin 16.3 gm., white blood count 13,000, and a normal differential. Urinalysis demonstrated 3 to 4 plus albumin, specific gravity 1.020, and occasional leukocytes and granular casts. The remainder of renal function studies were normal.

On the day of admission the patient remained cyanotic and disoriented. He was given penicillin, bronchodilators and mercurial diuretics with no apparent change in his condition. Digitalization was begun on the second hospital day. Oxygen was administered intermittently and on several occasions the patient was noted to become semi-stuporous. Arterial blood gas studies demonstrated marked oxygen unsaturation, a low pO_2 and high pCO_2. (Table II.) It was believed that the patient showed no signs of improvement with routine therapy, and actually seemed worse while receiving oxygen. Because of this a Drinker-Collins respirator was used in an effort to produce adequate ventilation during oxygen administration. While the patient was in the respirator, arterial blood gas studies demonstrated decrease in anoxia without increase in hypercapnia. (Table II.)

The patient was treated during the next four days with oxygen and the respirator, during which time there was a progressive improvement with disappearance of cyanosis, clearing of the mental processes and a decrease in signs and symptoms of congestive heart failure.

TABLE III

ARTERIAL GAS STUDIES IN CASE III BEFORE, DURING AND FOLLOWING RESPIRATOR THERAPY

		CO_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pH direct	pH calc.
9/26/51	(a) Breathing oxygen continuously	72.6	21.1	88.1	69	93	7.21	7.25
	(b) Breathing room air	71.2	21.3	47.0	19	70	7.35	7.36
	(c) Breathing room air, in respirator	67.7	20.1	58.3	31	74	7.34	7.32
	(d) Breathing oxygen in respirator	67.2	20.4	90.7	83	75	7.28	7.31
	(e) Breathing oxygen, in respirator, plus suction and vaponephrine	66.0	20.4	83.4	78	65	7.29	7.35
9/28/51	(a) After 48 hours in respirator: breathing O_2	61.6	21.0	78.1	46	57	7.36	7.39
	(b) Breathing room air, out of respirator	65.3	21.0	69.0	39	54	7.40	7.43
	(c) Breathing O_2, out of respirator	64.5	20.4	90.6	90	60	7.39	7.40
10/10/51	Following recovery: Breathing room air	44.7	22.2	83.3	59	45	7.36	7.34

Further arterial studies revealed a decrease in the pCO_2 and CO_2 content of the blood and an increase in the pO_2 and oxygen saturation. (Table II.) The patient was removed from the respirator and oxygen therapy was discontinued. He continued to improve and gradually resumed full activities. One month later complete pulmonary function studies were performed demonstrating the typical pattern of severe emphysema. (Tables V and VI.)

CASE III. A fifty-nine year old white male accountant was admitted on September 22, 1951, with severe cough and dyspnea. For thirty years the patient had noted chronic cough which was frequently productive, along with bouts of bronchitis. He smoked two packages of cigarettes daily. Three years prior to admission exertional dyspnea and wheezing developed. Ten days prior to admission, following an upper respiratory infection, there was an increase in the cough and dyspnea and development of ankle edema. On physical examination there were marked dyspnea and cyanosis. Temperature was 99°F., pulse 112 and blood pressure 110/80. Examination of the chest revealed an increase in the anteroposterior diameter and restriction of motion of the chest cage. There was dullness to percussion and many coarse rales at the right base and diminished breath sounds throughout. Examination of the heart revealed no abnormalities other than a loud second pulmonic sound. There was moderate ankle edema and minimal clubbing of the fingers.

X-ray of the chest revealed severe generalized emphysema and a pneumonic consolidation at the right base. Electrocardiogram was compatible with right ventricular hypertrophy. The hemogram and blood chemistries were normal.

For the first three days of hospitalization the patient was treated with intermittent oxygen, antibiotics in the form of penicillin and aureomycin and bronchodilators. There was a low grade fever. He remained cyanotic when out of the oxygen tent and moderate amounts of purulent sputum were noted. On September 25, 1951, he was noted to be extremely confused after several hours in an oxygen tent and rapid improvement followed removal from it.

On the fourth hospital day arterial blood gas studies were performed and confirmed the clinical impression of CO_2 retention and decom-

pensated acidosis as a result of prolonged oxygen administration. (Table III.) The patient was placed in a Drinker-Collins respirator and oxygen was administered continuously by nasal catheter. The pharynx was aspirated at frequent intervals. Bronchodilators and penicillin were continued. After approximately two hours in the respirator it was noted that a large quantity of secretions was being raised. Wheezing and pulmonary congestion diminished and the patient had improved symptomatically. After forty-eight hours the respirator and oxygen therapy were discontinued and the patient continued to do well. Arterial gas studies reflected the clinical improvement. (Table III.)

Complete pulmonary function studies were performed two weeks later, demonstrating the pattern of severe emphysema. (Tables V and VI.)

TABLE IV

ARTERIAL GAS STUDIES IN CASE IV BEFORE AND AFTER ARTIFICIAL RESPIRATION

Date		CO_2 Content (vol. %)	O_2 Capacity (vol. %)	O_2 Saturation (%)	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	pH calc.
6/1/51	Breathing room air (comatose) before use of PBR	59.3	22.2	39.2	26	96	7.14
6/4/51	Breathing room air, before use of respirator	62.4	20.1	87.6	55	57	7.40
7/19/51	Breathing room air, following recovery	58.3	19.2	92.3	66	69	7.29

CASE IV. A fifty-six year old Puerto Rican male was admitted on May 24, 1951, with dyspnea of three weeks' duration and productive cough for one week. In 1921 the patient had pleurisy. In 1946 he was refused employment because of an abnormal chest x-ray. He had noted intermittent wheezing and dyspnea for three years before admission and ankle edema for two years.

At the time of admission the patient's temperature was 103°F., the pulse 116. He was orthopneic and cyanotic. Poor expansion of the chest bilaterally with more limitation on the right was noted. There was dullness to percussion over the lower half of the right lung field and at the left base, diminished breath sounds and tactile fremitus over these areas, moist rales at the left base and occasional wheezing over the right upper lung field. The pulmonic second heart sound was accentuated. The liver was two fingerbreadths below the right costal margin. There was a suggestion of ascites and there was moderate peripheral edema.

Blood count on admission revealed a normal white blood count and differential, red blood count 6 million, hemoglobin 18.5 gm., hematocrit 62 per cent. A chest roentgenogram revealed extensive bilateral pleural calcification and moderate cardiac enlargement. An electrocardiogram was consistent with right ventricular hypertrophy. Venous pressure was 280 mm. of water, decholin circulation time 15 seconds, ether time 10 seconds.

The patient was treated with penicillin and bed rest for the first five days with no change in the clinical picture. On the fifth hospital day digitalization was begun and oxygen was administered intermittently by mask. Later that day the patient was noted to be semi-stuporous. He was placed in an oxygen tent and treated with mercurial diuretics. Shortly thereafter he became comatose although cyanosis diminished. The stupor persisted until the patient was removed from the oxygen tent for routine care the next day. It was believed at this time that the patient was in severe respiratory acidosis and that this was aggravated by oxygen therapy. In order to alleviate this artificial respiration in the form of the pneumatic balance resuscitator was applied. Within one hour there was clearing of the mental processes and disappearance of cyanosis. Artificial respiration was discontinued later that day, and the patient maintained satisfactory clinical progress for the next forty-eight hours. Arterial blood gas studies (Table IV) reflected this improvement. Although the patient was fairly comfortable at this time, it was believed that oxygen therapy was still indicated because of moderate anoxia. Artificial respiration was reinstituted by means of a Drinker-

Collins respirator and oxygen was administered by nasal catheter. This was continued intermittently for one week, along with antibiotics, bronchodilators and treatment of cardiac decompensation. On June 12, 1951, respirator and oxygen therapy were discontinued. The patient was relatively asymptomatic and all signs of congestive heart failure had disappeared. Fluoroscopy at that time revealed bilateral pleural calcification, no motion of the rib cage, restriction of diaphragmatic motion and only minimal enlargement of the left ventricular outflow tract. Complete pulmonary function studies were performed one month later and these revealed marked impairment of ventilation. (Tables v and vi.)

TABLE V

LUNG VOLUMES AND VENTILATION FOLLOWING RECOVERY FROM ACUTE ILLNESS

Case No.	Predicted Vital Capacity (cc.)	Observed Vital Capacity (cc.)	Predicted Residual Air (cc.)	Observed Residual Air (cc.)	Alveolar Nitrogen (%)	Residual Air / Total capacity (%)	M.B.C. (%)
I	4,020	1,795	1,295	3,875	2.49	65.6	35
II	3,990	1,605	1,290	3,090	9.30	61.7	15
III	4,020	1,970	1,300	3,700	9.04	65.6	16
IV	3,800	900	1,220	880	<2.5	41.7	42

TABLE VI

BLOOD AND GAS STUDIES FOLLOWING RECOVERY FROM ACUTE ILLNESS

Case No.	O_2 Saturation at Rest (%)	O_2 Saturation after Exercise (%)	pO_2 (mm. Hg)	pCO_2 (mm. Hg)	A-A* Gradient with Room Air (mm. Hg)	Dead Space (in % of tidal air)
II	88.9	....	69	57	16	55
III	83.3	....	59	45	40	43
IV	92.3	84.6	66	69	4	56

* In Cases II and III the gradient was higher with greater oxygen concentrations in the inspired air and normal with low mixtures.

RESULTS AND COMMENTS

It is apparent from the clinical histories and pulmonary function studies that these patients had chronic pulmonary disease with variable degrees of pulmonary insufficiency. Functional studies in the first three cases revealed a clear-cut emphysema pattern. (Tables v and vi.) While Case iv also had long-standing pulmonary disease, the functional pattern was that of ventilatory insufficiency without significant abnormalities of the alveolar-arterial oxygen gradients (Tables v and vi) and without any evidence of emphysema. In view of this and the calcified pleurae and restriction of chest cage motion on fluoroscopy, it is believed that the patient's anoxia and hypercapnia was on the basis of defective diaphragmatic and chest wall bellows action. The definitive studies of pulmonary function were made following complete recovery from acute illness, and it is reasonable to assume that the results are representative of the basic functional picture of these patients.

Analysis of the case histories reveals that in each case a superimposed pulmonary infection was the initial event in the development of the acute phase. This infection was usually in the nature of a bronchitis with superimposed bronchopneumonia. Case III, in addition, had x-ray evidence of lobar involvement. It is of interest to note that, with the exception of Case IV, these patients were either afebrile or ran a low-grade fever. Similarly, except for transient leukocytosis in Case II, the white cell count was usually normal and therefore recognition of the infection was made even more difficult. Anoxia and profound cyanosis had developed by the time of admission to the hospital and definite symptoms and signs of cardiac failure were noted.

The recognition of this clinical picture of acute anoxia which has been precipitated by acute bronchial infection in patients with chronic pulmonary insufficiency can present a difficult diagnostic problem. For example, the diagnoses considered in Case I were: congenital heart disease with a right to left shunt because of the severe cyanosis, acute pulmonary infarction, and even pericardial effusion with tamponade to account for the right-sided heart failure.

The presence of bronchitis and emphysema was overlooked initially because of the patient's relatively short history of dyspnea and his ability to do hard physical labor. Because of the failure to recognize the clinical problem in this case the rational therapy employed in the other three cases was not utilized, thus prolonging the acute stage.

Initial arterial blood gas studies revealed in all cases profound anoxia, hypercapnia and variable degrees of respiratory acidosis. (Tables I to IV.) Continuous oxygen therapy was employed in all cases. In Case I the stupor became more pronounced, in Case IV coma was precipitated. In Cases II and III, in addition to mental confusion, arterial gas studies demonstrated a rise in the pCO_2 and decompensated respiratory acidosis. This syndrome of so-called carbon dioxide narcosis may be produced by relatively short periods of exposure to oxygen. Case IV, for example, became comatose after only two hours in an oxygen tent. Analysis of our results does not permit the determination of the level of CO_2 retention at which O_2 therapy will become dangerous, as these patients had varying degrees of anoxia, hypercapnia and elevation of total plasma bicarbonate. Blood chloride levels as modified by the state of renal function will also obviously influence the picture.

Results with Artificial Respiration. The need for some form of therapy that will relieve anoxia without subjecting the patient to the danger of carbon dioxide narcosis is apparent. Simultaneous artificial respiration and continuous O_2 therapy met this need.

Cases II and III demonstrate the effectiveness of the Drinker-Collins respirator in increasing the effective alveolar ventilation to levels sufficiently high to minimize respiratory acidosis even when oxygen is administered. (Tables II and III.) For example, Case II, while receiving O_2 without the respirator, had a rise in pCO_2 from 75 mm. to 87 mm. of mercury and a concomitant drop in pH. (Table II.) This was prevented when the respirator was in operation. In both cases the striking clinical improvement noted within forty-eight hours was reflected in the blood gases. (Tables II and III.)

It is not to be inferred that these marked changes are the result of artificial respiration alone. These patients were also treated intensively for bronchial infection and obstruction with antibiotics and bronchodilators. Nevertheless, the results in Cases II and III are in striking contrast to those of Case I. In the latter case the failure to utilize artificial respiration and bronchodilators undoubtedly contributed to prolongation of the acute stage.

In addition to the mechanical effects of artificial respiration in providing more effective ventilation, we have observed that the respirator tends to promote bronchial drainage and thus maintain a more adequate airway. This was very striking in Case III. After only two hours in the respirator large amounts of secretion were raised and physical examination of the chest revealed improved ventilation.

The pneumatic balance resuscitator in a cooperative or sufficiently comatose patient may serve the same purpose as a Drinker-Collins respirator. For example, Case IV demonstrated a striking clinical improvement in several hours when this apparatus was used as an emergency measure to combat the coma induced by continuous oxygen therapy. Examination of later data (Table IV) demonstrated that the improved oxygenation and diminished acidosis can be entirely attributed to the use of the pneumatic balance resuscitator. The subsequent use of the Drinker-Collins respirator did not effect further clinical or physiologic improvement.

OBSERVATIONS

Pathogenesis of the Syndrome. This group of patients is representative of the usual case of pulmonary insufficiency due to emphysema that one sees in everyday practice. This, or any similar group, will on clinical examination show inadequate bellows motion of the chest and bronchial obstruction secondary to chronic bronchial infection. These factors plus difficulty in proper distribution of gases result in alveolar-respiratory insufficiency.[7] This leads to a chronic state of ineffective alveolar ventilation characterized by arterial anoxia and hypercapnia and the arterial pH may be decreased. Such patients are very susceptible to repeated bouts of acute bronchitis and bronchopneumonia, which are usually successfully treated with penicillin or other antibiotic therapy. In an occasional patient the degree of bronchial obstruction due to infection will be so severe that effective alveolar ventilation will be further diminished, leading to acute anoxia and carbon dioxide retention. We have observed the precipitation of the first episode of cardiac failure at this time in these patients and in several others under our care.

These patients undoubtedly have chronic

pulmonary artery hypertension, as manifested by large pulmonary arteries on x-ray, loud second pulmonic sounds and electrocardiographic evidence of right ventricular hypertrophy. Anoxia has been implicated as one of the mechanisms responsible for pulmonary artery hypertension. Motley and co-workers[8] have demonstrated that 10 per cent oxygen inhalation will produce significant increases in pulmonary artery pressures in normal individuals. This has been confirmed in normals and in patients with emphysema.[9] It is reasonable to assume that the acute right heart failure in our cases can be explained by just such a mechanism. The case histories reveal, furthermore, that the patients' first manifestation of decompensation occurred following an episode of acute bronchitis. In each patient arterial gas studies performed at the time of the acute infection revealed profound anoxia. In Case III there was demonstrated a complete disappearance of signs of congestive heart failure in twenty-four hours, during which time no specific therapy was directed at this condition. This can be attributed to relief of anoxia by oxygen therapy, artificial respiration, bronchodilators and antibiotics.

The final sequence in the development of this clinical picture occurs with the placing of such a patient in an environment of high oxygen concentration. It is now well recognized that respiratory acidosis due to further retention of carbon dioxide occurs and that the mechanism undoubtedly is the removal, by relief of anoxia, of the stimulus to ventilation, operating through the carotid receptor mechanism.[10] For a more complete discussion the reader is referred to the recent paper of Boutourline-Young and Whittenberger.[1]

In these patients it has been quite striking to observe the rapid onset of stupor, and even coma, on exposures to oxygen sometimes of only two hours. Conversely, upon withdrawal of these patients from high oxygen concentrations a rapid clearing of mental symptoms occurs. In all cases the onset of symptoms could be correlated with hypercapnia and acidosis. It is not possible to state the exact mechanism in the production of mental symptoms for it is conceivable that the acidosis *per se* may contribute to them. It is tempting, nevertheless, to implicate excessive carbonic acid in the pathogenesis of the abnormal cerebral state. It is known that hypocapnia will produce cerebral vasoconstriction and hypercapnia increases cerebral blood flow.[11] The latter may, in turn, explain the phenomenon of increased spinal fluid pressure which has been occasionally observed in severe emphysema.[12] Papilledema has been described in such cases.[13]

Therapeutic Rationale. It is obvious that a successful therapeutic approach based upon physiologic considerations should include the production of an adequate airway and improvement of effective alveolar ventilation. It is apparent from our cases that infection, with excessive secretion and possible accompanying bronchial spasm, is the major factor in diminishing the airway. Control of the infection with adequate antibiotic therapy, particularly penicillin, is of primary importance at the onset. The use of bronchodilators such as the aerosol epinephrines is helpful.

There is no question, in view of the cyanosis, that oxygen therapy is necessary and this should be instituted immediately, with extreme care taken to observe the patient's ventilation and mental responses. When possible, arterial gas studies should be performed. If these analyses cannot be done, serial observation of the carbon dioxide combining power should be made, a rise indicating probable increasing respiratory acidosis. If there is noted increasing mental stupor or confusion, decrease in ventilation, a significant increase in the arterial pCO_2 or decrease in pH while receiving oxygen, artificial respiration is indicated immediately. Its efficacy in increasing effective alveolar ventilation has already been commented upon. In addition, as previously noted, the respirator is also valuable in the mechanical removal of bronchial secretions. If a respirator is readily available it should probably be used at the onset of therapy instead of waiting for the unfavorable signs that may be produced by oxygen alone. Our experiences with the various types of artificial respirators leads us to believe that the Drinker-Collins variety is satisfactory. The patient tends to be more relaxed in it and, in addition, it has the advantage of permitting frequent aspiration of pharyngeal secretion without interfering with the administration of oxygen by nasal catheter. The pneumatic balance resuscitator, on the other hand, requires an extremely cooperative or a comatose patient and must be removed in order to aspirate the pharynx. If means for artificial respiration are not available, the use of intermittent oxygen therapy may serve as a compromise measure.

The response of cardiac failure to the treatment regimen has already been mentioned. Although we have noted a rapid response without the use of digitalis, this drug should be employed when indicated.

Pneumoperitoneum has been advocated[14] in the treatment of chronic pulmonary emphysema. A recent report[15] indicated the successful application of pneumoperitoneum in combating respiratory acidosis in patients similar to those described by us. It may be worth while, in the absence of any form of artificial respirator, to institute pneumoperitoneum as an emergency procedure in such situations. We do not believe, however, that this form of therapy has been evaluated sufficiently in either situation to warrant its routine use.

SUMMARY AND CONCLUSIONS

1. Four cases of chronic pulmonary disease are cited to illustrate how infection can precipitate acute anoxia, respiratory acidosis and cardiac failure.

2. The clinical picture common to these cases is described. Fever and leukocytosis are frequently absent. There is usually evidence of right heart strain and pulmonary artery hypertension, and cardiac failure is often observed for the first time.

3. The production of respiratory acidosis and mental confusion by relatively short periods of oxygen therapy is described.

4. A therapeutic rationale based upon physiologic considerations is outlined. This includes treatment of bronchial obstruction and infection, oxygen therapy and artificial respiration as indicated.

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REFERENCES

1. Boutourline-Young, H. J. and Whittenberger, J. L. The use of artificial respiration in pulmonary emphysema, accompanied by high carbon dioxide levels. *J. Clin. Investigation*, 30: 838, 1951.
2. Van Slyke, D. D. and Neill, J. M. Determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.*, 61: 523, 1924.
3. Riley, R. L., Proemmel, D. D. and Franke, R. E. A direct method for determination of oxygen and carbon dioxide tensions in blood. *J. Biol. Chem.*, 161: 621, 1945.
4. Baldwin, E. deF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. 1. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
5. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D. and Franke, R. E. Experimental analysis in man of oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. *Am. J. Physiol.*, 147: 199, 1946.
6. Van Slyke, D. D. and Sendroy, J., Jr. Studies of gas and electrolyte equilibria in blood. xv. Line charts for graphic calculations by the Henderson-Hasselbalch equation, and for calculating plasma carbon dioxide content from whole blood content. *J. Biol. Chem.*, 79: 781, 1928.
7. Baldwin, E. deF., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency, iii. Study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
8. Motley, H. L., Cournand, A., Werko, L., Himmelstein, A. and Dresdale, D. The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *Am. J. Physiol.*, 150: 315, 1947.
9. Westcott, R. N., Fowler, N. O., Scott, R. C., Hauenstein, V. D. and McGuire, J. Anoxia and human pulmonary vascular resistance. *J. Clin. Investigation*, 30: 957, 1951.
10. Comroe, J. H., Jr. and Schmidt, C. F. Part played by reflexes from carotid body in chemical regulation of respiration in dog. *Am. J. Physiol.*, 121: 75, 1938.
11. Schmidt, C. F. The Cerebral Circulation in Health and Disease. Springfield, Ill., 1950. Charles C. Thomas.
12. Davies, C. E. and MacKinnon, J. Neurological effects of oxygen in chronic cor pulmonale. *Lancet*, 2: 883, 1949.
13. Simpson, T. Papilloedema in emphysema. *Brit. M. J.*, 2: 639, 1948.
14. Carter, M. G., Gaensler, E. A. and Kyllonen, A. Pneumoperitoneum in the treatment of pulmonary emphysema. *New England J. Med.*, 243: 549, 1950.
15. Callaway, J. J. and McKusick, V. A. Carbon dioxide intoxication in emphysema: emergency treatment by artificial pneumoperitoneum. *New England J. Med.*, 245: 9, 1951.

Pulmonary Function Studies in Bronchial Asthma*

I. In the Control State

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There have been many thorough studies during the past two decades dealing with various pulmonary function studies in patients with pulmonary emphysema, fibrosis, tuberculosis, etc.[1–13] Until recently no comprehensive pulmonary function studies have been reported in patients with classical bronchial asthma in the control and treated state.

Hurtado et al.[14] studied the total lung capacity and its subdivisions in six patients during acute bronchial asthma. Five of these patients were restudied immediately after the administration of epinephrine subcutaneously and the sixth patient two days after spontaneous recovery from acute asthma. These investigators found a decreased vital capacity and an increased residual volume and functional residual capacity during acute asthma, which improved after epinephrine or by spontaneous recovery. The residual volume *approached* normal values. One patient was given an injection of epinephrine two days after feeling well; "no appreciable changes in pulmonary capacity" were noted.

Baldwin[15] studied ten asthmatic patients during an asthma-free period. She reported an increase in the alveolar nitrogen after seven minutes of oxygen, a decrease in the maximum breathing capacity, and hyperventilation. The total lung capacity, residual volume, residual volume to total lung capacity ratio and arterial blood gases were normal.

Whitfield et al.[16] reported on the effect of ephedrine in ten "emphysematous subjects with bronchospasm (i.e., asthmatics)." Nine of these patients had complete lung volume measurements. These patients were "obviously asthmatic—audibly wheezing—full of rhonchi." The mean absolute values before and after therapy were reported without the predicted normal values for that group. Ephedrine caused statistically significant improvement in vital capacity, inspiratory capacity and residual volume, moderate improvement in expiratory reserve volume, and slight, statistically not significant decrease in total lung capacity and functional residual volume. Other reports have dealt with selected pulmonary function studies only, such as the vital capacity and/or maximum breathing capacity, air velocity index, walking ventilation or a few measurements of lung volume.[17–20]

The pulmonary function studies in this report were carried out in a group of patients suffering primarily from bronchial asthma. Patients with chronic pulmonary emphysema and secondary bronchospastic crises were not included in this series. The procedures were performed only when the patients felt "quite well" or were completely asymptomatic. These criteria were established because of the unreliability of some of the determinations in the acutely asthmatic patient. We were primarily concerned with the nature of the underlying defect in the asthmatic subject during a period of well being. Our second aim was to record the site and nature of improvement effected by treatment.

CASE MATERIAL

Most of the patients used in this study were well known to our laboratory, having been subjects for various studies related to bronchial asthma for one or more years. A total of forty-

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two patients were studied, many of them two or more times. Their ages ranged from fifteen to seventy-two years; there were fifteen females and twenty-seven males and the duration of their asthma ranged from four months to forty-two years. All but two patients suffered from perennial bronchial asthma, many of them with seasonal exacerbations. The essential data are listed in Table 1.

Outline of Studies Performed. The following determinations were made: (1) Resting ventilation and tidal air, (2) spirometric determinations of expiratory reserve volume, inspiratory capacity, vital capacity, maximum breathing capacity; (3) maximum expiratory velocity; (4) functional residual capacity, residual volume, total lung capacity, index of intrapulmonary mixing; (5) arterial blood gas analyses (CO_2

TABLE 1

Case	Age, Sex	Body Surface (M^2)	Duration of Asthma (yr.)	Comments
1. A. D.	35, F	1.73	4	Non-seasonal; several severe attacks; had ACTH treatment
2. H. B.	35, M	2.35	20	Non-seasonal; mild to moderately severe
3. J. F.	37, M	1.77	36	Non-seasonal; symptom-free for 7 years
4. M. G.	25, F	1.74	14	Non-seasonal; severe in past year; several courses of ACTH
5. J. H.	33, M	1.71	33	Non-seasonal; severe asthma recently
6. W. S.	18, M	2.04	16	Non-seasonal; fairly severe, especially in winter
7. A. B.	29, M	1.84	½	Preceded by bronchitis for many years
8. E. M.	42, F	1.58	24	Non-seasonal; mild in past 1½ yr.
9. L. F.	39, F	1.72	15	Non-seasonal; mild to moderately severe
10. P. D.	43, M	1.86	23	Non-seasonal; mild in past 1½ yr.
11. L. A.	64, M	1.69	3	Non-seasonal; moderately severe
12. G. W.	43, F	1.26	12	Perennial with exacerbations in Aug.–Sept.
13. D. I.	44, M	1.66	15	Non-seasonal; mild
14. M. G.	53, M	2.05	13	Non-seasonal; mild
15. L. B.	16, M	1.57	16	Perennial during last year; mild
16. A. McG.	42, F	1.67	9	Non-seasonal; mild; occasionally severe
17. L. B.	18, F	1.50	13	Frequent severe exacerbations; non-seasonal
18. A. N.	52, M	1.65	14	Non-seasonal; frequent exacerbations
19. N. Z.	33, M	2.11	6	Spring and winter mostly; mild
20. M. L.	27, F	1.49	25	Non-seasonal; continuous and severe since Aug. 1949; several courses of ACTH
21. J. M.	53, M	1.72	1	Progressively severe since Dec. 1949
22. M. E.	59, F	1.64	30	Continuous and progressively severe; several courses of ACTH
23. F. V.	50, M	2.05	5	Non-seasonal; mild
24. J. B.	40, F	1.76	15	Mild with exacerbations on exposure to cats and dogs
25. B. R.	18, F	1.75	9	Seasonal (fall and winter); severe
26. C. V.	45, M	1.99	4	Mild, but progressive
27. J. M.	43, M	2.06	42	Non-seasonal; intermittent, mild
28. E. A.	15, M	1.54	8	Moderately severe; mainly in summer and fall
29. P. C.	13, F	1.57	6	Non-seasonal; progressively severe
30. M. C.	42, M	1.63	16	Non-seasonal; frequent severe attacks
31. B. B.	40, M	1.97	10	Mild; sensitive to feathers
32. C. T.	50, M	1.85	⅔	Progressively severe; 9 gm. ACTH; well since Dec. 1950
33. C. M.	16, M	1.80	14	Non-seasonal; no asthma for 2 yr. until 1951
34. E. S.	17, F	1.47	1½	First attack on day of mother's funeral who had had asthma; progressively severe since Sept. 1950
35. J. F.	34, M	1.55	32½	Non-seasonal; exacerbation in winter; ACTH treatment; well for 1½ mo.
36. C. C.	54, M	1.60	10	Non-seasonal; exacerbation in winter, more difficulty lately
37. J. G.	29, M	1.88	½	Hay fever in 1948; asthma in 1949
38. D. I.	42, F	1.74	4	Mild; summer and fall mostly
39. J. K.	72, M	2.02	1	Mild; well since ACTH in June 1950
40. W. McC.	57, M	2.09	15	Non-seasonal; mild; intermittent
41. J. S.	65, M	1.98	25	Non-seasonal; frequent exacerbations, well 1 yr.
42. E. W.	22, F	1.52	22	Non-seasonal; moderately severe; frequent exacerbations

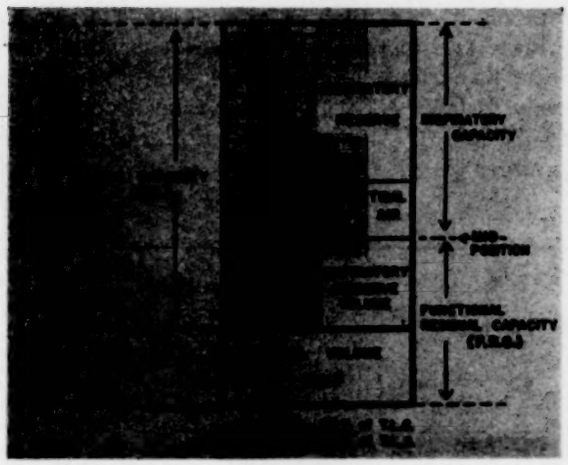

FIG. 1. Subdivisions of the total lung capacity and terminology used throughout text.

and O_2) at rest and after one minute exercise. All or part of these measurements were repeated after treatment: (1) aminophyllin 0.5 gm. i.v., or (2) bronchodilator aerosols, six inhalations.

Figure 1 depicts the subdivisions of the total lung capacity and the terminology used throughout our text.[21]

Technic. 1. After a twenty- to thirty-minute period of bed rest the resting ventilation was measured for five minutes, employing a J-valve and a recording gasometer. The respiratory rate was counted and the tidal volume obtained from these determinations.

2. Arterial blood was obtained by puncture of the radial artery. First a "resting sample" was drawn, and the needle was left in place. The "post-exercise sample" was obtained after the patient had performed thirty steps up and down a 20 cm. platform during one minute. The blood was analyzed for O_2 and CO_2 by the Van Slyke method.[22]

3. Ventilometric studies were then performed with the patient in the sitting position. A Collins spirometer of 9 L. capacity was used. The soda lime canister was eliminated in order to decrease the resistance to the flow of air, and the spirometer bell filled with room air. Carbon dioxide accumulation was prevented by flushing the bell with room air after each single determination.

All ventilometric components were repeated at several minutes' interval until at least two determinations were of the same magnitude and maximal. The maximum breathing capacity (MBC) was performed after the completion of part 4. This is advisable inasmuch as forceful or rapid breathing may initiate or aggravate bronchospasm in a previously comfortable asthmatic subject. The MBC was executed in the standing position and performed for twelve seconds.

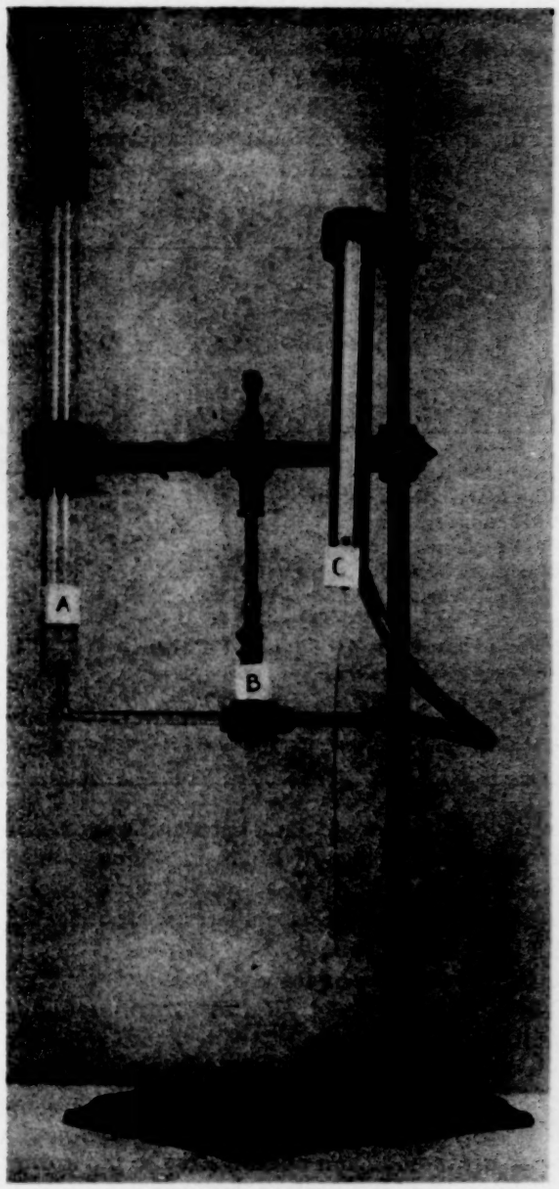

FIG. 2. Apparatus for estimation of the maximum expiratory velocity. A, glass tube and disposable mouthpiece through which the person blows forcefully; B, a horizontal narrow tube which transmits the impact of air from A to C; C, a calibrated tube with a light weight float.

4. Alveolar gas samples, determinations of functional residual capacity (FRC) and the index of intrapulmonary mixing (Index) were obtained in the sitting position. We employed the open circuit method with 100 per cent

oxygen as described by Darling et al.[23] The apparatus used was essentially as described by these authors, except for the use of Douglas bags for collection of the lung washings instead of a Tissot spirometer. Alveolar samples were obtained by the method of Haldane and Priestley at the end of a forced expiration and collected in a previously evacuated gas sampling tube.[24] The Haldane tube has at its distal end a one-way flutter valve. Gas analyses were made by the Scholander technic.[25]

5. Maximum expiratory velocity (MEV): The instrument used for this determination is represented in Figure 2.* The patient was instructed to place the mouthpiece (top part of A) about 1 inch inside his mouth and blow instantaneously and forcefully. The buccal muscles were prevented from adding force to the flow of air by putting the mouthpiece inside the mouth, rather than placing the lips against the opening. The impact of airflow is partly transmitted via a narrow tube (B) to a flowmeter (C) which contains a light float. The flowmeter has a scale reading in millimeters which is transposed to read liters per second according to calibration curves. The reading thus represents the maximum volume forcefully exhaled per second.

TABLE II

Determination	Normal Values	Bronchial Asthma			
		Average	Range	No. of Determinations	No. of Subjects
Inspiratory capacity	75–80% of V.C.	2.439		75	42
Expiratory reserve volume	20–25% of V.C.	1.145		75	42
Vital capacity		3.584		75	42
% of predicted vital capacity	116	100	51–158	75	42
Maximum breathing capacity (L./min.)		65.4		70	39
% of predicted maximum breathing capacity	106	62.9	11–130	70	39
Resting ventilation (L./min./M^2 b.s.)	3.2–3.6	5.42	3.11–7.52	48	32
Index of intrapulmonary mixing (% alveolar N_2)	<2.5	4.05	1.0–12.12	53	35
Residual volume (L.)		3.242		53	35
Total lung capacity		6.917		53	35
% of predicted total lung capacity	120.8	125.8	78–176	53	35
RV/TLC × 100	<30	47.0	35–67	53	35

RESULTS

In Table II are listed the results of the studies. The lung volumes are expressed in liters, the maximum breathing capacity in liters per minute and in per cent of predicted value, the resting ventilation in liters per minute per M^2 body surface. All volumes have been corrected to BTPS (37°c. and 760 mm. barometric pressure).

1. *Vital Capacity.* A wide range of fluctuation in vital capacity was obtained in the same patients at different times during the periods of well being. This may be seen in Figure 3. A variation as high as 2 L. was observed in several patients. Many of the patients, regardless of the duration of their asthma, had vital capacities of 4 L. or higher.

Since these determinations do not take into consideration sex, age and size of the patient, the same determinations are also expressed in per cent of predicted values. The prediction formulas are those of Baldwin et al.[7]

Males: $[27.63 - (0.112 \times \text{age})] \times \text{Height in cm.}$

Females: $[21.78 - (0.101 \times \text{age})] \times \text{Height in cm.}$

Although these prediction formulas for the vital capacity are for measurements in the supine position, while our patients were studied in the sitting position, we did not correct for this small difference. In the sitting position the vital capacity is about 5 per cent larger than in the lying position; this amounts only to about 100 to 200 cc.[1,26,27]

These formulas are not too satisfactory since

* Constructed and calibrated for us by Fischer and Porter Co., Hatboro, Pa.

all normal subjects and many asthmatic patients were found to have vital capacities greater than 100 per cent of predicted. We obtained an average value of 116 per cent of predicted normal for ten normal subjects. The value obtained in our asthmatic patients usually fell below this level; seventeen determinations were greater than 116 per cent. The vital capacity ranged between 51 and 158 per cent of predicted values; thirty-seven of the seventy-five determinations were 100 per cent or over, and the average value for seventy-five determinations on forty-two patients was 100.1 per cent of predicted normal.

When the patients were classified according to the degree of wheezing in the lungs at the time of the studies, the results were as follows: Those with clear lungs gave an average value of 112.8 per cent; those with 1+ wheezing, 102.1 per cent; and those with 2+ wheezing, 95.2 per cent of predicted. (Fig. 5.)

2. *Inspiratory Capacity and Expiratory Reserve Volume.* The average values of seventy-five determinations in forty-two asthmatic subjects for these measurements were 2.44 L. inspiratory capacity and 1.15 L. expiratory reserve volume. In normal subjects the inspiratory capacity constitutes approximately 75 to 80 per cent of the vital capacity, the expiratory reserve volume. 20 to 25 per cent. In our patients these ratios were 68 and 32 per cent, respectively, of the average 3.58 L. vital capacity. These ratios were within normal range in only fourteen determinations on ten patients.

3. *Maximum Breathing Capacity (MBC).* Multiple determinations of the MBC were made. Expressed in per cent of predicted values, they

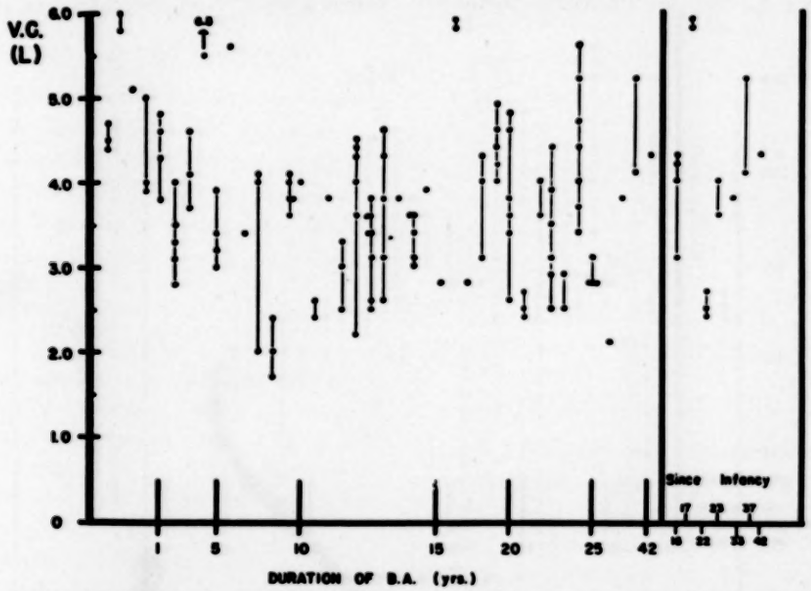

FIG. 3. Vital capacity in liters, plotted according to the duration of bronchial asthma. Multiple determinations on the same patient are connected by vertical lines.

are represented graphically in Figure 4. We used the following prediction formulas:[7]

Males: $[86.5 - (0.522 \times \text{age in years})] \times M^2 \text{ body surface}$

Females: $[71.3 - (0.474 \times \text{age in years})] \times M^2 \text{ body surface}$

The MBC of seven normal control subjects yielded an average value of 106.3 per cent of the predicted normal value with these formulas. In thirty-nine asthmatic patients the average value of seventy determinations was 62.9 per cent of the predicted normal value. Only five determinations in five patients were over 100 per cent, of which three were greater than 106.3 per cent. A wide fluctuation in MBC was noted when measured at various times in the same patient. It will be observed from Figure 4 that the longer the duration of the asthma, the lower the MBC tends to be. The six patients who have had asthma since infancy were found to have a MBC of less than 81 per cent of the predicted normal value. (Fig. 4.)

When the patients were classified according to the chest findings, the average values were

75.0 per cent for those with clear lungs; 51.8 per cent for those with 1+ wheezing; and 46.6 per cent of the predicted normal for those with 2+ wheezing. (Fig. 5.)

4. *Resting Ventilation.* The resting minute ventilation for normal adults is given as 3.6 L. for males and 3.2 L. per sq. m. body surface for females.[27] In our asthmatic patients we obtained an average value of 5.42 L. per sq. m. (forty-eight determinations on thirty-two patients). As seen among normals, there was a large individual variation.

5. *Index of Intrapulmonary Mixing* (*Index*). The normal range for the index of intrapulmonary

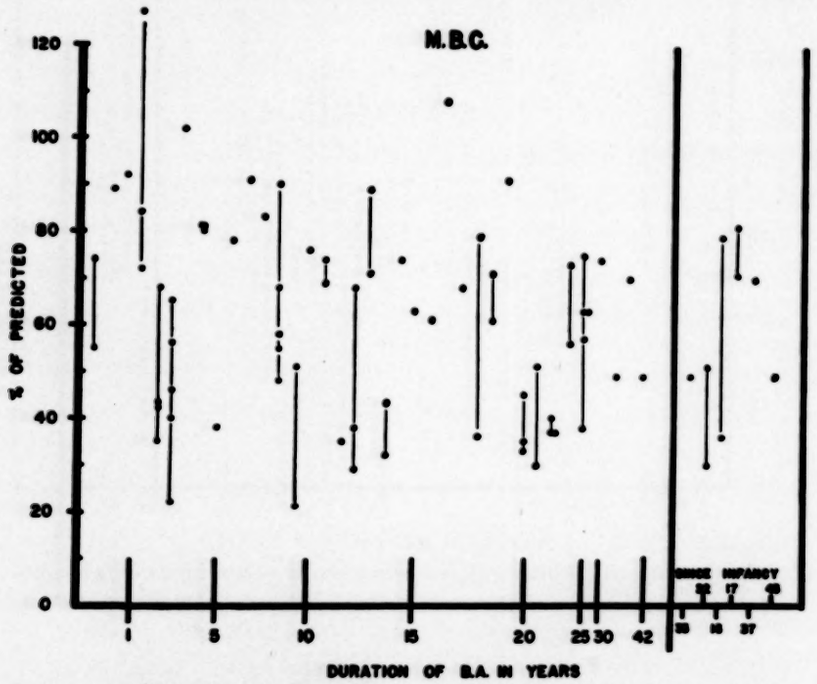

FIG. 4. Maximum breathing capacity in per cent of predicted normal value plotted according to the duration of bronchial asthma. Multiple determinations on the same patient are connected by vertical lines.

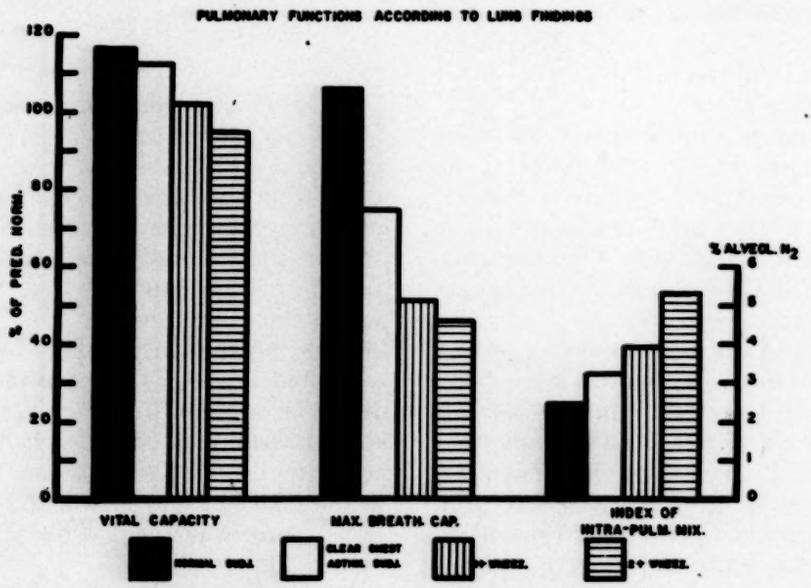

FIG. 5. Correlation between lung findings (wheezing) and such tests as vital capacity, maximum breathing capacity and intrapulmonary mixing.

mixing is up to 2.5 per cent alveolar N_2 after seven minutes breathing of 100 per cent oxygen. Table II shows that the range found in fifty-three determinations on thirty-five asthmatic subjects was from 1.0 to 12.12 per cent, with an average value of 4.05 per cent N_2. The ten patients studied by Baldwin[15] had a mean value of 4.5 per cent N_2.

Classifying the patients according to the chest findings, we see from Figure 5 that those with a clear chest had an average of 3.26 per cent N_2; those with 1+ wheezing had 3.95 per cent; and those with 2+ wheezing, 5.34 per cent N_2.

6. *Total Lung Capacity (TLC).* The prediction for total lung capacity is based on the ratio of vital capacity to the total lung capacity. Thus the formula most widely used is $\frac{\text{vital capacity}}{a}$ where "a" represents 80 for the ages sixteen to thirty-four years, 76.6 for thirty-five to forty-nine years and 69.2 for the ages of fifty to sixty-nine years.[26] Using the observed vital capacity for this calculation will give an expected total lung capacity of approximately normal size only when dealing with a normal vital capacity. Because one usually obtains an abnormal vital capacity when dealing with pulmonary disease, other investigators modified this formula and used the predicted normal vital capacity to calculate the predicted normal lung capacity.[28] Although this modification of the formula is justified in principle, the resultant figures are not satisfactory because, as we have previously pointed out, the predicted vital capacity is usually much smaller than the observed vital capacity in normal subjects as well as in many of our asthmatic patients. When we used this modified prediction formula for total lung capacity, we obtained an average value of 124.6 per cent of predicted for the normal subjects and 153.8 per cent of predicted for our asthmatic patients. To circumvent the difficulty of obtaining too small a predicted total lung capacity by using the latter formula, or of obtaining a varying total lung capacity based on a widely fluctuating vital capacity in asthmatic patients, we decided to calculate the predicted total lung capacity by using the largest vital capacity actually obtained on the patient either before or after treatment. If the highest reading was smaller than the predicted vital capacity, the latter figure was considered in the formula.

Under these circumstances we obtained for five normal control subjects a total lung capacity which was 120.8 per cent of predicted and for thirty-five asthmatic subjects an average value of 125.8 per cent of predicted total lung capacity. (Table II.) Of the fifty-three determinations on thirty-five patients, there were thirty-one determinations on twenty-three patients greater than 120.8 per cent, the value we obtained for our normal subjects.

TABLE III
RESIDUAL VOLUME/TOTAL LUNG CAPACITY × 100

Ages	Normal Values	Asthmatic Subjects	No. of	
			Subjects	Determinations
16–34	20.0	48.6	13	20
35–49	23.4	46.4	14	19
50–69	30.8	45.7	8	14
All patients		47.0	35	53

7. *Residual Volume (RV) and Residual Volume to Total Lung Capacity Ratio (RV/TLC).* As with other subdivisions of the lung, the residual volume varies greatly from person to person according to sex, age and size. However, the residual volume bears a fairly constant relationship to the lung capacity, and the ratio: residual volume to total lung capacity has significance.

TABLE IV

Duration of Asthma (yr.)	$\frac{RV}{TLC} \times 100$	TLC (% of Predicted)	
		Average	Range
5	43.0	112.3	93.6–130.6
6–10	43.2	120.0	108.3–134.3
11–20	48.8	130.0	110.8–165.0
20	50.2	134.6	110.0–176.5

In Table III we have listed the normal ratios according to the various age groups and the findings in the asthmatic subjects.[26] All subjects showed a marked elevation, almost identical when the average values for the three age groups are compared: 48.6 per cent, 46.4 per cent and 45.7 per cent for the ages sixteen to thirty-four, thirty-five to forty-nine and fifty to sixty-nine years, respectively. The average value of fifty-three determinations for the thirty-five asthmatic patients was 47.0 per cent.

In Table IV these residual volume/total lung capacity ratios have been arranged according to the duration of asthma. These data do not take into consideration the severity of the asthma. However, the data show that the longer the duration of asthma, the more severe the disturbance in the residual volume to total lung capacity relationship.

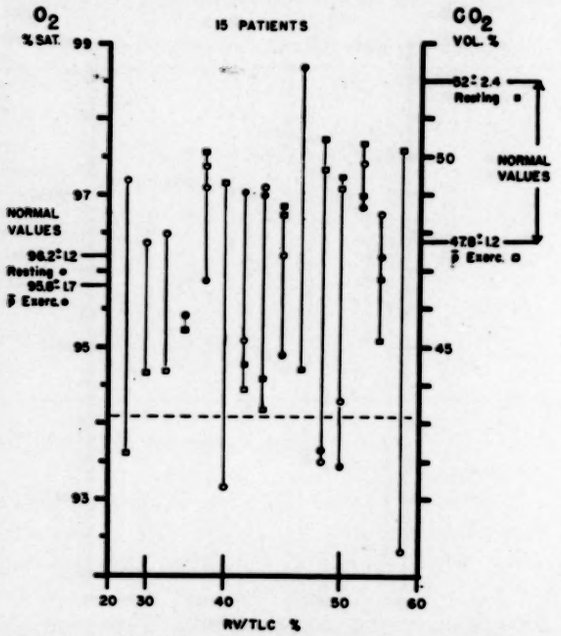

FIG. 6. Arterial blood oxygen (per cent saturation) and carbon dioxide (volume per cent) plotted according to the RV/TLC ratio in fifteen patients with bronchial asthma. The horizontal broken line indicates the lowest range of normal oxygen saturation after exercise.

8. *Arterial Blood Gases.* In Figure 6 are charted oxygen per cent saturation and carbon dioxide volume per cent of arterial blood before and after exercise in fifteen patients. Most of the patients gave normal oxygen saturations, and none had retention of carbon dioxide. Low oxygen saturation either before or after exercise was recorded in patients 20 (M. L.), 21 (J. M.) and 25 (B. R.). Clinically these patients were among our most handicapped and showed other evidence of pulmonary insufficiency as well.

9. *Maximum Expiratory Velocity.* The lowest reading obtained in fifty normal control subjects was 7.5 L./second; the majority blew between 8 and 10 L./second. (Fig. 7.) Among thirty-one asthmatic subjects, only four of forty-one determinations were 7.5 L./second or higher. The average value for this group of patients was 3.9 L./second.

COMMENTS

The *vital capacity* measurement has been used for a long time as a test of pulmonary efficiency. In recent years, however, investigators have emphasized the poor correlation between vital capacity on the one hand and pulmonary disability and pulmonary disease on the other. It is not uncommon, especially in emphysema, to obtain a high vital capacity in a patient whose other function studies indicate marked impairment.[5,9] We encountered many asthmatic patients with a vital capacity within the range or in excess of the predicted normal value.

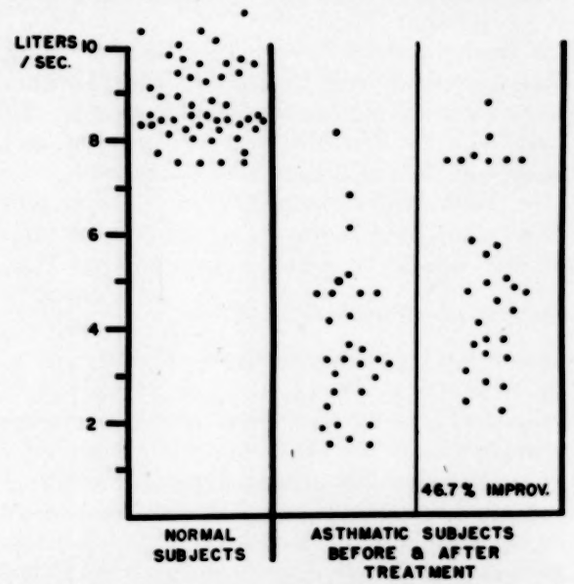

FIG. 7. The maximum expiratory velocity in normal subjects is 7.5 L. per second or greater. In asthmatic subjects the velocity is usually less than 7.5 L. per second.

Thus the vital capacity is a poor measure of ventilatory insufficiency and has little value in detecting impairment in the patient with subclinical asthma, i.e., when the lungs are clear. The average value obtained in our asthmatic subjects with a clear chest was 112.8 per cent of the predicted normal value, which is well within the range of normal. (Fig. 5.)

The shortcoming of the vital capacity as a pulmonary function test lies in the fact that it does not measure function but volume without relation to time; it is static and not dynamic.[20] Clinically, ventilatory efficiency depends largely on volume-time relationship. However, the vital capacity can be a useful test in studying bronchial asthma if the time factor for its performance is considered. This can be done conveniently

by obtaining a spirographic tracing of the vital capacity, analyzing the slope of the tracing and measuring it in relation to time.[29] Using a high speed on the spirometer, the distance between the heavy lines on the paper can be divided into equal parts to represent one-second intervals. The inspiratory as well as expiratory volumes per second can be measured.

Figure 8 illustrates the tracing of a vital capacity of 1,848 cc. Measured off in seconds, the performance was 546, 504, 294 and 210 cc. in each consecutive second. After the use of bronchodilator aerosols the vital capacity was 3,045 cc. and the volume-time performance improved to 1,281, 756, 420 and 210 cc. for consecutive seconds.

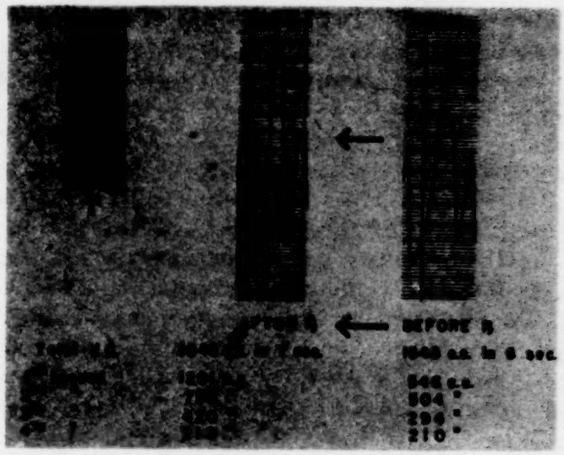

FIG. 8. Spirographic tracing of a vital capacity before and after treatment with bronchodilator aerosols. The transparency T is placed over the tracing and the volume exhaled during each second is measured.

The *inspiratory capacity*, instead of constituting 75 to 80 per cent of the vital capacity as in normal subjects, was decreased to 68 per cent. This upward shift in "mid-position" (base line at end of normal expiration) was seen in patients with decreased as well as with normal vital capacities. This shift in mid-position is the so-called "high inspiratory position" commonly found in patients with emphysema.[2,3] The *expiratory reserve volume*, as a rule, will be normal or increased since it is increased to an average of 32 per cent of the vital capacity; it will be smaller than normal only when the vital capacity is much decreased.

Hurtado et al.[14] similarly found during acute bronchial asthma that of the divisions of the vital capacity the inspiratory capacity is affected most, usually with an increase of the expiratory reserve volume. During asthma they found that the inspiratory capacity to vital capacity ratio ranged between 54.1 and 80.0 per cent and the expiratory reserve volume to vital capacity ratio between 20.0 and 45.9 per cent.

Producing obstruction to expiration experimentally results in a decreased inspiratory capacity as well as an increased residual volume and functional residual capacity.[30]

The *maximum breathing capacity*, in contrast, is a test of dynamic function. Of the many factors affecting this function, air-flow resistance (patency of the bronchi, tissue "viscance" and turbulence) is the most important in patients with pulmonary obstructive disease, such as bronchial asthma. We know from clinical as well as experimental studies that performance of the maximum breathing capacity test is greatly affected by the patency of the tracheobronchial tree[31] and by changes which cause turbulence in air-flow.[32] Proctor et al.[32] demonstrated that in normal respiratory air-flow, turbulence may appear at speeds of 60 to 75 L. per minute, but that in patients with pulmonary disease, turbulence will develop at velocities of only 20 to 30 L. per minute. Changes in the tracheobronchial passages, mucus or secretions may cause turbulence in air-flow, limiting the production of high flow velocities required for normal performance of the maximum breathing capacity or maximum expiratory velocity tests.

The MBC has its limitations because it requires the patient's cooperation perhaps more than any other test. The patient has to be able and willing to perform and to repeat this rather exhausting procedure. However, when reliably performed, it is a significant test in the study of bronchial asthma, especially in detecting subclinical asthma. Patients with a clear chest performed an average of 75 per cent of predicted normal; only five of the thirty-nine patients had an MBC greater than 100 per cent. Of the patients with 1+ and 2+ wheezing none had an MBC over 100 per cent of predicted. The vital capacity did not show such constant correlation with chest findings. In Figure 5 we see the correlation between chest findings and the maximum breathing capacity.

The *resting ventilation* was found to be increased. This finding was also observed by Baldwin[15] in her asthmatic patients during an asthma-free period. Increased ventilation at rest and after moderate exertion is also seen in patients with pulmonary emphysema and fibrosis.[3] No satisfactory explanation for this phenomenon is

available. The increase in resting ventilation, together with the decreased MBC, accounts for the markedly diminished ventilatory reserve of such patients.

The *index of intrapulmonary mixing* is considered to reflect primarily adequacy of ventilation of the alveoli. Uneven ventilation will result in a high index[7,15,23] High values will therefore be found in patients with severe emphysema who ventilate unevenly and have large residual volumes. However, in the asthmatic, although the average index was elevated (4.05 per cent N_2), we found many patients with a normal index in the presence of a high RV/TLC ratio. Other factors which influence the rate of nitrogen dilution seem to be of greater importance in bronchial asthma. Bronchial and bronchiolar patency must be taken into consideration. This becomes evident from Figure 5; the patients with a clear chest gave an average value of 3.25 per cent; those with 1+ wheezing 3.95 per cent; and those with 2+ wheezing 5.34 per cent N_2.

Another factor involved is the effective minute ventilation. It is obvious that with a greater ventilation there will be a faster nitrogen dilution from the lungs (i.e., a lower index at the end of seven minutes' oxygen breathing). Wolfe and Carlson[28] studied mixing efficiency of the lungs by a method (electronic nitrogen analyzer) taking into consideration the variations in minute volume. They found that a diseased lung may have poor mixing efficiency yet attain normal nitrogen percentage at the end of seven minutes by means of hyperventilation.

The influence on the index of both the bronchiolar patency and the minute ventilation becomes further evident by the changes observed after treatment (see Part II).

The *RV/TLC ratio* was high in all determinations and, among our patients, this figure seems to correlate with the duration of asthma better than any of the other pulmonary functions. (Table IV.) This is in disagreement with the findings of Hurtado et al.[2]

Of the thirty-five asthmatic patients studied, twenty-three showed a total lung capacity greater than the average value of 120.8 per cent of predicted which we obtained for normal subjects. The average value for asthmatic subjects was 125.8 per cent of predicted, which is slightly greater than for the normals. Thus it can be said that 65 per cent of the patients with bronchial asthma have an enlarged lung capacity. The degree of enlargement of the total lung capacity appears also to be related to the duration of asthma. (Table IV.) The RV/TLC ratio, as well as the total lung capacity, is greater than normal but the total lung capacity to a lesser degree than the ratio; therefore, the residual volume must be enlarged to a greater degree than the total lung capacity. These findings are in disagreement with those of Baldwin.[15] She studied ten asthmatic subjects during an asthma-free period and found the residual volume, total lung capacity and RV/TLC ratios within normal limits. Her report does not indicate, however, how long the patients had been free of asthma, whether the patients were, perhaps, seasonal asthmatics only, or how severe their illness was. Our patients, with the exception of two, were perennial asthmatics with frequent non-seasonal or seasonal severe exacerbations. However, we are also studying patients during a prolonged period of remission, eight months and longer. Those studied so far have shown a total lung capacity within normal range of prediction but an enlarged residual volume and a high RV/TLC ratio. (Details of this study will be the subject of a subsequent report.)

If by the term emphysema is meant an enlarged RV/TLC ratio due to an increase in residual volume, with or without an increase in total lung capacity as well, without requiring evidence of impaired diffusion of gases across the alveolar membrane, we must conclude that all patients with chronic bronchial asthma have emphysema. If the severity of emphysema is indicated by the RV/TLC ratio, as stated by Hurtado et al.[2] and Borden et al.,[33] most of our patients have severe emphysema, regardless of the duration of their asthma. However, if diffusion difficulty, CO_2 retention and/or O_2 unsaturation, is considered as a determining factor (Baldwin et al.[9]), most of our patients have mild emphysema.

SUMMARY*

Pulmonary function studies were performed in forty-two patients with chronic bronchial asthma at a time when they were symptomatic. The results may be summarized as follows: (1) The vital capacity ranged between 51 and 158 per cent of predicted normal value; the inspiratory capacity: vital capacity ratio aver-

* For references in both articles, see Part II, page 34.

aged 68 per cent. (2) The maximum breathing capacity ranged between 11 and 130 per cent of predicted normal value. (3) The resting ventilation was generally increased, and ranged between 3.11 and 7.52 L. per minute per square meter body surface. (4) The index of intrapulmonary mixing ranged between 1.0 and 12.12 per cent nitrogen. (5) The total lung capacity averaged 125.8 per cent of predicted normal value. The residual volume: total lung capacity ratio ranged between 35 and 67 per cent and averaged 47.0 per cent. (6) The maximum expiratory velocity averaged 3.9 L. per second.

Pulmonary Function Studies in Bronchial Asthma*

II. After Treatment

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Aminophyllin given by various routes and bronchodilator aerosols have been accepted as among the most important therapeutic agents in the treatment of bronchial asthma. Numerous and varied are the laboratory studies with these agents in bronchial asthma, usually dealing with vital capacity, and occasionally with MBC. Pulmonary function studies in asthmatic patients have been reported before and after subcutaneous epinephrine[14] and before and after oral ephedrine.[16] In the present intravenous studies aminophyllin† and adrenergic bronchodilator[34] sprays‡ were used.

TECHNIC

The studies were repeated after treatment on the same morning of the previously described basal testing. Treatment consisted of (1) aminophyllin, 0.5 gm. in 20 cc. solution given intravenously over a five-minute period. (The spirometric determinations were performed fifteen to thirty minutes after the injection, followed by the functional residual capacity determination); or (2) bronchodilator sprays, six inhalations, given about ten minutes before beginning the repeat studies and again before measuring the functional residual capacity.

RESULTS

Vital Capacity. The average percentage of improvement in thirty-one determinations on twenty-four patients following intravenous aminophyllin was 10.6 per cent; the maximum improvement observed was 40 per cent. With bronchodilator aerosols, the average improvement in thirty-six determinations on twenty-nine patients was 16.9 per cent; one patient (the same as mentioned previously) showed a maximum improvement of 187 per cent. Expressing the vital capacity in per cent of predicted normal values, intravenous aminophyllin changed their vital capacity from 104.7 to 114.1 per cent; bronchodilator aerosols produced a change from 102.2 to 116.3 per cent of predicted normal. (Tables I and II, Fig. 1.)

In the aminophyllin-treated group the inspiratory capacity, constituting 66 per cent of the vital capacity or 2.47 L. before treatment, increased to 2.68 L., or 67 per cent of the vital capacity. Similarly, in the bronchodilator aerosol-treated patients, the inspiratory capacity increased from 2.30 to 2.46 L., or from 64 to 65 per cent of the vital capacity. The changes in the expiratory reserve volume following treatment were from 34 to 33 per cent and from 36 to 35 per cent of the vital capacity after aminophyllin and bronchodilator aerosols, respectively. (Fig. 2.)

Maximum Breathing Capacity. An average improvement of 30.9 per cent was observed in twenty-eight determinations on twenty-two patients following the administration of intravenous aminophyllin. An average improvement of 50.0 per cent followed the use of bronchodilator aerosols in thirty-five determinations on twenty-eight patients.

Expressing the MBC in per cent of predicted normal values, intravenous aminophyllin increased this value from 65.2 to 82.3 per cent,

† Kindly supplied by G. D. Searle and Company.

‡ The preparation used was neosuprel,® 2½ per cent, kindly supplied by Winthrop-Stearns Co.

* From the Department of Inhalational Therapy, Boston City Hospital, and the Department of Medicine, Tufts College Medical School, Boston, Mass.

and following bronchodilator aerosols this value increased from 62.6 to 85.7 per cent of predicted normal. (Tables I and II, Fig. 1.)

Resting Ventilation. From Tables I and II we see that the majority of patients experienced an increase in the resting minute ventilation after treatment. After intravenous aminophyllin the average value increased from 5.66 to 6.04 L./minute/m^2 body surface; fourteen of the nineteen determinations on fourteen patients had increased. After bronchodilator aerosols the average value changed from 5.76 to 6.00 L/minute/m^2 body surface; six of eight determinations on eight patients showed this increase in resting ventilation.

Index of Intrapulmonary Mixing. The average value for the index among the patients studied was 4.05 per cent N_2. After intravenous aminophyllin the average value was reduced to 2.22 per cent N_2, and after bronchodilator aerosols, to 2.97 per cent N_2. The improvement in the index went as high as 66.5 per cent in one patient. Following intravenous aminophyllin the average improvement was 32.7 per cent in twenty determinations in seventeen patients and 28.8 per cent after bronchodilator aerosols in thirteen determinations on thirteen patients. (Tables I and II, Fig. 1.)

Total Lung Capacity. Our normal control subjects had a total lung capacity of 120.8 per cent of predicted value. Twenty determinations in seventeen patients were made before and after intravenous aminophyllin; their total lung capacity changed from an average of 7.310 to 7.370 L., or from 128.2 to 129.3 per cent of predicted normal. Thirteen determinations were made in thirteen asthmatic patients before and after bronchodilator aerosols; their total lung capacity changed from an average of 6.492 to 6.518 L., or from 125.9 to 126.8 per cent of predicted normal. In the intravenous aminophyllin-treated group eleven of the twenty determinations showed improvement; one did not change; and the remaining eight showed an increase in total lung capacity. In the aerosol-treated group seven of the thirteen determinations showed a decrease; the remaining six, an increase in the total lung capacity after treatment. (Tables I and II, Fig. 2.)

TABLE I

Determination	Aminophyllin i.v.		% Change		No	
	Before	After	Average	Range	Determinations	Subjects
Vital capacity (L.)	3.676	4.031	+10.6	−10 to +40	31	24
% of predicted V.C.	104.7	114.1	.....	.....	31	24
% of predicted MBC	65.2	82.3	+30.9	−8 to +108	28	22
Resting ventilation (L./min.)	5.66	6.04	.....	.....	19	14
Index intrapulmonary mixing (% N_2)	4.05	2.22	−32.7	−65 to +21	20	17
Residual volume (L.)	3.591	3.387	.....	.....	20	17
Total lung capacity (L.)	7.310	7.371	.....	.....	20	17
% of predicted T.L.C.	128.2	129.3	.....	.....	20	17
RV/TLC × 100	49.7	46.3	−7.4	−28 to +12	20	17

Residual Volume and Residual Volume to Total Lung Capacity Ratio. In Table III are listed the residual volume and total lung capacity ratios before and after treatment, divided according to age groups. All three groups show an over-all slight improvement after treatment. However, of thirty-three determinations only twenty-three were improved, while the remaining ten ratios became higher with treatment.

In Tables I and II we have listed the changes in RV/TLC ratio after intravenous aminophyllin and bronchodilator aerosols separately. After intravenous aminophyllin the change ranged from +12 to −28 per cent with an average value of −7.4 per cent. Bronchodilator aerosols resulted in changes ranging from +4 to −24 per cent with an average decrease of −8.1 per cent. (Fig. 1.)

The residual volume decreased in twelve of the twenty tests and remained unchanged in one test after intravenous aminophyllin; the average value changed from 3.590 to 3.387 L. After bronchodilator aerosols ten of the thirteen

patients showed a decrease in the residual volume measurement; the average value changed from 2.930 to 2.744 L. (Fig. 2.)

Maximum Expiratory Velocity. The maximum expiratory velocity was tested in nine patients before and after intravenous aminophyllin. The average velocity rose from 3.2 L./second to 4.1 L./second. The average improvement was 30.6 per cent.

The maximum expiratory velocity was tested in sixteen patients before and after bronchodilator aerosols. The average velocity rose from 4.0 L./second to 6.0 L./second. The average improvement was 58.5 per cent. (Fig. 1.)

TABLE II

Determination	Bronchodilator Aerosols		% Change		No	
	Before	After	Average	Range	Determinations	Subjects
Vital capacity (L.)	3.490	3.940	+16.9	−15 to +187	36	29
% of predicted V.C.	102.2	116.3	.....	.....	36	29
% of predicted MBC	62.6	85.7	+50.0	−10 to +147	35	28
Resting ventilation (L./min.)	5.76	6.00	.....	.....	8	8
Index intrapulmonary mixing (% N_2)	4.41	2.97	−28.8	−66 to +15	13	13
Residual volume (L.)	2.930	2.744	.....	.....	13	13
Total lung capacity (L.)	6.492	6.518	.....	.....	13	13
% of predicted T.L.C.	125.9	126.7	.....	.....	13	13
RV/TLC × 100	45.7	42.7	−8.1	−24 to +4	13	13

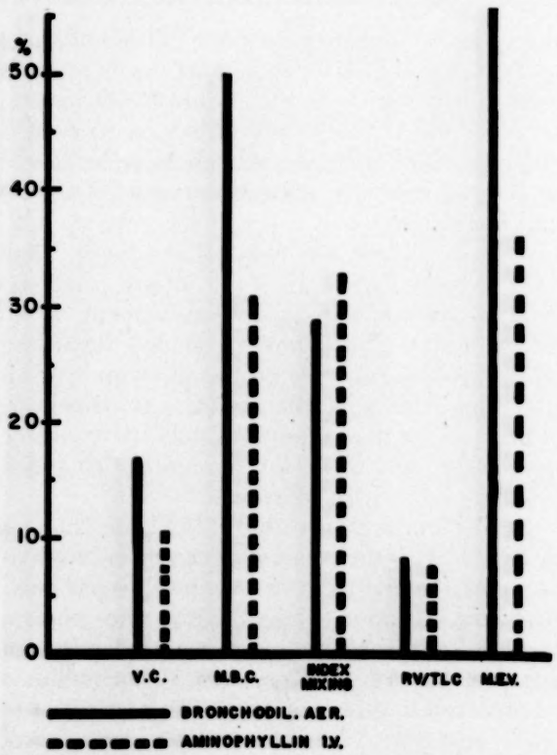

FIG. 1. Summary of per cent improvement after treatment.

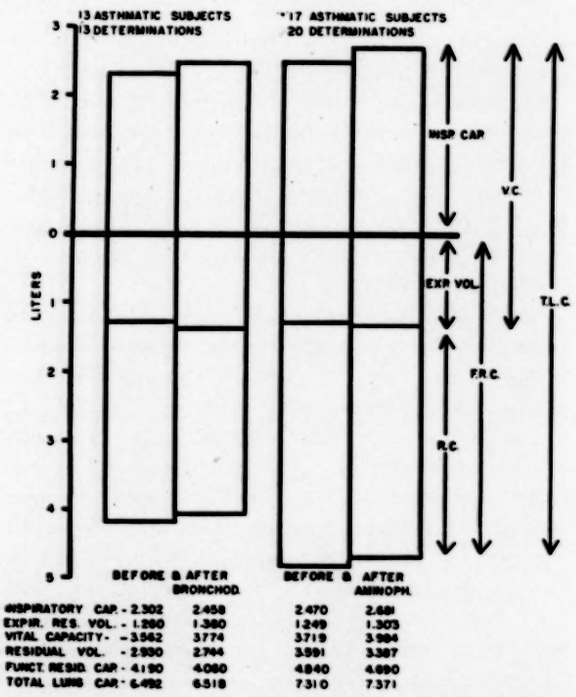

FIG. 2. Changes in lung volumes after treatment. The lung volumes are measured from the mid-position as zero line.

COMMENTS

Since the *vital capacity* shows little impairment in most asthmatic patients, the degree of improvement with treatment will be small, 10.6 per cent of improvement with intravenous amino-

phyllin and 16.9 per cent with bronchodilator aerosol. This slight degree of improvement suffices to restore the vital capacity to within the normal range in most asthmatic subjects; 114.1 per cent and 116.3 per cent of predicted vital capacity. Twelve patients with lungs clear to auscultation showed an average improvement in their vital capacity of 9 per cent.

The upward shift in mid-position was seen in most of our asthmatic patients. Although treatment improved the absolute values of both the inspiratory capacity and expiratory reserve volume, the abnormal ratio of these to the vital capacity remained essentially unchanged. In other words, this defect appeared to be a static one. However, in patients with *acute* bronchial asthma after treatment with subcutaneous epinephrine the inspiratory capacity to vital capacity ratio improved from a range of 54.1 to 80.0 per cent to a range of 60.8 to 83.0 per cent.[14] Thus it appears that the actual size of the inspiratory capacity will improve with treatment in acute as well as subacute asthma as long as there is relief of bronchial obstruction; the relative size of the inspiratory capacity changes significantly only with acute asthma (severe bronchoconstriction).

The *maximum breathing capacity* showed an average improvement of 30.9 per cent after intravenous aminophyllin and rose to 82.3 per cent of predicted normal value. After bronchodilator aerosols the improvement was 50.0 per cent and the MBC increased to 85.7 per cent of predicted normal value. The ten patients studied by Baldwin[15] during an asthma-free period showed a mean value of 58 per cent of predicted MBC, which rose to 81 per cent of predicted normal after aerosol treatment. It is of some interest that there was a 26 per cent improvement among the patients with clear lung fields; in the patients with 1+ and 2+ wheezing respirations, the improvement was 40 and 53 per cent, respectively. Even though the MBC does not closely approach normal values with treatment, the degree of improvement is considerable. This greatly improved ventilatory reserve must be an important contribution to the clinical improvement.

A concomitant of this improved function is, no doubt, the improvement in *index of intrapulmonary mixing*, which averaged 32.7 per cent after intravenous aminophyllin and 28.9 per cent after bronchodilator aerosol. This degree of improvement in the index of mixing, in the face of minimal improvement in residual volume and residual volume/total lung capacity ratio, in our opinion indicates that bronchial and bronchiolar obstruction is of greater influence than the size of the residual volume in determining this index. The relationship between minute ventilation and index of mixing is indicated by the changes observed after treatment. With a few exceptions, most patients had an increase in the minute ventilation, and there was improvement of the abnormally high index in all of these.

The *maximum expiratory velocity* also showed a degree of improvement of the same order as observed in the maximum breathing capacity and index; there was an average improvement of 30.6 per cent with aminophyllin and 58.5 per cent with bronchodilator aerosols. Here, too, we believe that bronchial patency and turbulence play a more important role since, as we will soon see, these abnormalities are probably the only "reversible" abnormal pulmonary functions in the chronic asthmatic.

Otis and Proctor[35] measured alveolar pressures with simultaneous rate of flow of respired air in human subjects. These investigators found that an average pressure of 1.8 cm. of water is required to produce a flow of air of 0.5 L. per second. In our asthmatic subjects we found the maximum expiratory velocity markedly decreased to an average of 3.9 L. per second which improved greatly after treatment. The decreased maximum air flow in the asthmatic undoubtedly is not due to a decreased alveolar pressure but to inability to force the normal amount of air through passages which are narrowed and cause turbulence. Likewise, the improvement after treatment can best be explained on the basis of diminished bronchoconstriction and less turbulence, and not by any increase in alveolar pressure.

The *resting ventilation* usually increased after treatment. Yet, the ventilatory reserve improved considerably, and this was entirely due to the great increase in maximum breathing capacity.

The *total lung capacity* after treatment showed changes which were small and variable in direction, and probably due to inherent errors in technic. After intravenous aminophyllin the total lung capacity increased an average of 0.8 per cent, and after bronchodilator aerosols it increased an average of 0.4 per cent. Hurtado et al.,[14] treating acute bronchial asthma with

epinephrine, obtained a decrease in total lung capacity. Whitfield et al.,[16] treating acute asthma with oral ephedrine, could not demonstrate any change in total lung capacity. We were not able to demonstrate reversibility of "emphysema" (high total lung capacity and high residual volume/total lung capacity ratios) in our asthmatic patients after treatment. Studies during prolonged periods of remission may shed more light on the reversibility of these defects. Such studies are in progress.

TABLE III

Ages	Residual Vol./Total Lung Capacity × 100			No.		
	Normal	Before Treatment	After Treatment	Subjects	Determinations	Improved Results
16–34	20.0	51.7	50.7	11	12	5
35–49	23.4	45.1	40.7	10	10	9
50–69	30.8	46.9	42.3	9	11	9
			Total	30	33	23

The *residual volume/total lung capacity ratios* show a negligible difference between the various age groups either before or after treatment. (Table III.) The changes observed with treatment are not startling either, an average improvement of 8.1 per cent after bronchodilator aerosols and 7.4 per cent after intravenous aminophyllin. There is lack of consistency in direction as well as in size of improvement of the residual volume/total lung capacity ratios with treatment. When improvement occurred, it was due to increase in the vital capacity in the face of a slight change in total lung capacity, this resulting in a decreased residual volume. (Fig. 2.)

By what mechanism does treatment allow an increase of the volume of the vital capacity within the limits of the rather static total lung capacity? Is it vascular? Some believe that the increase in vital capacity is due to a decrease of the pulmonary blood volume, as is seen following venesection[36] or following the injection of adrenalin which causes pulmonary vasoconstriction.[37,38] Although intravenous aminophyllin can be expected to effect pulmonary vascular changes, these would be in the nature of arteriolar dilatation.[38] Theoretically, this should give a decrease in vital capacity as well as in total lung capacity. On the other hand, it has been suggested that the improvement in vital capacity and residual volume after aminophyllin might be due to increased cardiac output.[39] The bronchodilator drug used in this study has very little cardiovascular effect.[40] If a small dose of six inhalations of this preparation has any adrenergic effect at all on the pulmonary vasculature, this change probably contributes little to the sizeable increases in the vital capacity. Is the increase in vital capacity after treatment due to the "opening-up" of a large number of bronchioles and alveoli contributing their volume to the measured increase in vital capacity? This simple explanation does not appear to be acceptable because not all cases showing an increase in vital capacity show also an increase in total lung capacity after treatment. However, this seeming discrepancy in changes in vital capacity and total lung capacity after treatment can be explained by the convincing experimental evidence for "collateral respiration."[41–43] Since it is possible for plugged-off lobules to participate in ventilation (gas exchange), the volume of such lobules will be measured at the time when the volume of the patent alveoli is measured (breathing 100 per cent oxygen for seven minutes). Reestablishing bronchial connections between these alveoli with the remainder of the lung will not change the total lung capacity significantly. However, during the short period of a vital capacity performance the alveoli with plugged bronchioles cannot contribute their volume through collateral ventilation channels. Patent airways are required for quick emptying of the alveoli when the vital capacity is estimated, and these are established by treatment.

Another mechanism must exist by which the vital capacity can increase, without similar changes in the total lung capacity, in the absence of secretions and occluded bronchioles. This mechanism is the degree of partial obstruction and resistance in the respiratory passages. A decrease of these would allow a more rapid emptying of a larger volume of air (vital capacity). We present this explanation despite the experimental work by Matheson et al.[31] showing that the vital capacity in *healthy* young adults was not affected by an increase in air flow resistance. The effect on muscular effort to overcome air flow resistance during a short lasting experiment can be expected to be different

from that in the patient with chronically increased resistance.

OBSERVATIONS

Pulmonary function studies of asthmatic patients at a time of comparative or complete comfort reveal slight impairment of vital capacity, marked decrease in maximum breathing capacity, as well as maximum expiratory velocity, a high index of intrapulmonary mixing, an enlarged total lung capacity and a high residual volume to total lung capacity ratio.

Treatment with either intravenous aminophyllin or bronchodilator aerosols indicates that some of these defects are rather static; improvement is of significant magnitude in maximum breathing capacity, maximum expiratory velocity and index; there is slight improvement of vital capacity and of residual volume to total lung capacity ratio; there is little improvement in inspiratory capacity to vital capacity ratio, and there is no decrease of total lung capacity.

SUMMARY

Pulmonary function studies were performed in forty-two patients with chronic bronchial asthma in the asymptomatic state after treatment which consisted of aminophyllin, 0.5 gm. intravenously, or neosuprel® bronchodilator, six inhalations by aerosol sprays.

Pulmonary function studies performed after treatment gave the following results. (1) The average improvement in the vital capacity was 10.6 per cent after aminophyllin and 16.9 per cent after bronchodilator aerosols. (2) The average improvement in the maximum breathing capacity was 30.9 per cent after aminophyllin and 50.0 per cent after bronchodilator aerosols. (3) The average improvement in the index of intrapulmonary mixing was 32.7 per cent after aminophyllin and 28.8 per cent after bronchodilator aerosols. (4) The average residual volume decreased slightly. The average total lung capacity did not change appreciably after treatment. (5) The average improvement in the residual volume to total lung capacity ratio was 7.4 per cent after aminophyllin and 8.1 per cent after bronchodilator aerosols.

Clinical and experimental data are discussed in relation to the possible mechanism involved in the pathologic physiology of bronchial asthma and the changes induced by treatment.

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REFERENCES

1. Hurtado, A. and Boller, C. Studies of total pulmonary capacity and its subdivisions. I. Normal, absolute and relative values. *J. Clin. Investigation*, 12: 793, 1933.
2. Hurtado, A., Kaltreider, N. L., Fray, W. W., Brooks, W. D. W. and McCann, W. S. Studies of total pulmonary capacity and its subdivisions. VI. Observations on cases of obstructive pulmonary emphysema. *J. Clin. Investigation*, 13: 1027, 1934.
3. Kaltreider, N. L. and McCann, W. S. Respiratory response during exercise in pulmonary fibrosis and emphysema. *J. Clin. Investigation*, 16: 23, 1937.
4. Cournand, A., Baldwin, E., Darling, R. C. and Richards, D. W., Jr. Studies on intrapulmonary mixture of gases. IV. The significance of the pulmonary emptying rate and simplified open circuit measurement of residual air. *J. Clin. Investigation*, 20: 681, 1941.
5. Goggio, A. F. The abnormal physiology of chronic pulmonary emphysema. *New England J. Med.*, 231: 672, 1944.
6. Ornstein, G. G. The value of pulmonary function tests in thoracic surgery for pulmonary tuberculosis. *Quart. Bull., Sea View Hosp.*, 8: 279, 1946.
7. Baldwin, E., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. I. Physiological classification, clinical methods of analysis, standard values in normal subjects. *Medicine*, 27: 243, 1948.
8. Baldwin, E., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. II. A study of thirty-nine cases of pulmonary fibrosis. *Medicine*, 28: 1, 1949.
9. Baldwin, E., Cournand, A. and Richards, D. W., Jr. Pulmonary insufficiency. III. A study of 122 cases of chronic pulmonary emphysema. *Medicine*, 28: 201, 1949.
10. Donald, K. W. and Christie, R. V. The respiratory response to carbon dioxide and anoxia in emphysema. *Clin. Sc.*, 8: 33, 1949.
11. Spain, D. M. Patterns of pulmonary fibrosis as related to pulmonary function. *Ann. Int. Med.*, 33: 1150, 1950.
12. Gaensler, E. A. and Carter, M. G. Ventilation measurements in pulmonary emphysema treated with pneumoperitoneum. *J. Lab. & Clin. Med.*, 35: 945, 1950.
13. Wright, G. W. and Filley, G. F. Pulmonary fibrosis and respiratory function. *Am. J. Med.*, 10: 642, 1951.
14. Hurtado, A. and Kaltreider, N. L. Studies of total pulmonary capacity and its subdivisions. VII. Observations during the acute respiratory distress of bronchial asthma and following the

administration of epinephrine. *J. Clin. Investigation*, 13: 1053, 1934.

15. Baldwin, E. Bronchial asthma. Combined Staff Clinics of Columbia University College of Physicians and Surgeons. *Am. J. Med.*, 1: 189, 1946.
16. Whitfield, A. G. W., Arnott, W. M. and Waterhouse, J. A. H. The effect of ephedrine in asthma and emphysema. *Quart. J. Med.*, 19: 319, 1950.
17. Warring, F. C., Jr. Ventilatory function. Experiences with a simple practical procedure for its evaluation in patients with pulmonary tuberculosis. *Am. Rev. Tuberc.*, 51: 432, 1945.
18. Gaensler, E. A. Air velocity index. A numerical expression of the functionally effective portion. *Am. Rev. Tuberc.*, 62: 17, 1950.
19. Gaensler, E. A. Ventilatory tests in bronchial asthma. *J. Allergy*, 21: 232, 1950.
20. Gray, J. S., Barnum, D. R., Matheson, H. W. and Spies, S. N. Ventilatory function tests. i. Voluntary ventilation capacity. *J. Clin. Investigation*, 29: 677, 1950.
21. Pappenheimer, J. R. Standardization of definitions and symbols in respiratory physiology. *Federation Proc.*, 9: 602, 1950.
22. Van Slyke, D. D. and Neill, J. M. The determination of gases in blood and other solutions by vacuum extraction and manometric measurements. *J. Biol. Chem.*, 61: 552, 561, 1924.
23. Darling, R. C., Cournand, A. and Richards, D. W., Jr. Studies on the intrapulmonary mixture of gases. ii. An open circuit method for measuring residual air. *J. Clin. Investigation*, 19: 609, 1940.
24. Haldane, J. B. S. and Priestley, J. G. Respiration. New Haven, Conn., 1935. Yale University Press.
25. Scholander, P. F. Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. *J. Biol. Chem.*, 167: 235, 1947.
26. Kaltreider, N. L., Fray, W. and Van Zile Hyde, H. The effect of age on the total pulmonary capacity and its subdivisions. *Am. Rev. Tuberc.*, 37: 662, 1938.
27. Comroe, J. H. Interpretation of commonly used pulmonary function tests. *Am. J. Med.*, 10: 356, 1951.
28. Wolfe, W. A. and Carlson, L. D. Studies of pulmonary capacity and mixing with the nitrogen meter. *J. Clin. Investigation*, 29: 1568, 1950.
29. Segal, M. S. and Herschfus, J. A. A simple method for the determination of vital capacity—time relationships. (In press.)
30. Lippelt, H. Einfluss der Stenosenatmung auf Lungenventilation und Lungenvolumina beim Gesunden. *Beitr. z. Klin. Tuberk.*, 81: 520, 1932.
31. Matheson, H. W., Spies, S. N., Gray, J. S. and Barnum, D. R. Ventilatory function tests. ii. Factors affecting the voluntary ventilation capacity. *J. Clin. Investigation*, 29: 682, 1950.
32. Proctor, D. E., Hardy, J. B. and McLean, R. Studies of respiratory air flow. ii. Observations on patients with pulmonary disease. *Bull. Johns Hopkins Hosp.*, 87: 225, 1950.
33. Borden, C. W., Russell, H. W., Ebert, R. V. and Wells, H. S. Pulmonary hypertension in chronic pulmonary emphysema. *Am. J. Med.*, 8: 701, 1950.
34. Herschfus, J. A., Bresnick, E., Levinson, L. and Segal, M. S. A new sympathomimetic amine (neosuprel) in the treatment of bronchial asthma. *Ann. Allergy*, 9: 769, 1951.
35. Otis, A. B. and Proctor, D. F. Measurement of alveolar pressure in human subjects. *Am. J. Physiol.*, 152: 106, 1948.
36. Plotz, M. Bronchial spasm in cardiac asthma. *Ann. Int. Med.*, 26: 521, 1947.
37. Sheldon, M. B. and Otis, A. B. Effect of adrenalin on resistance to gas flow in the respiratory tract and on the vital capacity of normal and asthmatic subjects. *J. Appl. Physiol.*, 3: 513, 1951.
38. Zimmerman, H. A. A study of the pulmonary circulation in man. *Dis. of Chest*, 20: 46, 1951.
39. Whitfield, A. G. W., Arnott, W. M. and Waterhouse, J. A. H. Effect of aminophyllin on emphysema. *Lancet*, 260: 490, 1951.
40. Laboratory Data, 1-(3,4-dihydroxyphenyl)-2-isopropyl-amino-1-butanol hydrochloride, "neosuprel." Winthrop-Stearns, Inc., New York.
41. Baarsma, P. R. and Dirken, M. N. J. Collateral ventilation. *J. Thoracic Surg.*, 17: 238, 1948.
42. Baarsma, P. R., Dirken, M. N. J. and Huizinga, E. Collateral ventilation in man. *J. Thoracic Surg.*, 17: 252, 1948.
43. Lindskog, G. E. Collateral respiration in the normal and diseased lung. *Yale J. Biol. & Med.*, 23: 311, 1951.

Paradoxical Result Obtained with the Hickey-Hare Test for Diabetes Insipidus*

With a Note on the Regulation of Chloride Excretion

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An objective test has been reported by Hickey and Hare[1] which distinguishes the polyuria of diabetes insipidus from that caused by the habitual ingestion of excessive amounts of water. We have encountered a paradoxical response in a patient with psychogenic polydipsia. A possible explanation for the response in this patient has been obtained by studying the response to the administration of pitressin.® The comparison of the response in this patient with that in a patient with typical diabetes insipidus is presented, together with a discussion of possible factors influencing chloride excretion.

METHODS

The procedure of Hickey and Hare was followed precisely except for the determination of glomerular filtration rates and, hence, chloride reabsorption. Plasma and urinary chlorides were determined either by a modified Volhard-Harvey procedure[2] or by the procedure of Van Slyke and Hiller.[3] Both the ratio for the urinary and plasma chloride (U/P) concentrations and the rate of urine flow per minute were determined for each fifteen-minute period.

CASE REPORTS

CASE I. S. W. was a twenty-four year old white, married female who had an insidious onset of polydipsia and polyuria two years prior to admission. Her fluid intake and output were approximately 15 L. a day. She had no significant organic or psychiatric difficulties prior to the onset of her present complaint. A physical and neurologic examination revealed no abnormalities. The urinalysis was normal except for a specific gravity of 1.001. PSP excretion was normal. Hematologic studies were also normal. X-rays of the skull revealed a normal pituitary fossa. The patient responded satisfactorily to nasal insufflation of posterior pituitary powder.

CASE II. M. D. was a twenty-two year old white, divorced female who was admitted to the hospital because of headaches and polydipsia. She had noticed the onset of polydipsia and polyuria of gradually increasing severity four months prior to admission and was drinking about 10 L. of fluid a day. She had no nocturia. Her response to pitressin was satisfactory. The past history reveals that she had a hysterical paralysis of her right arm two years prior to admission. Two weeks prior to the present admission she obtained a divorce and became emotionally disturbed. A complete physical examination was within normal limits. The urinalysis was negative except for the specific gravity of 1.003. A Fishberg concentration test revealed satisfactory concentration. Hematologic studies were normal. X-rays of the skull revealed a normal pituitary fossa.

RESULTS

CASE I. Figure 1 presents the data obtained. It will be seen that there was no significant change in the chloride U/P ratio during the period of sodium chloride loading. The rate of urine formation increased slightly. This is the typical response described by Hickey and Hare in patients with diabetes insipidus and represents a failure of the hypertonic saline to stimulate the output of the antidiuretic hormone.

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CASE II. Figure 2 presents the data obtained. It is obvious that the rate of urine formation decreased markedly during the period of sodium chloride loading. This is typical of the response of the normal person.[1] However, during the period of loading the chloride U/P ratio increased only slightly, a typical response in a patient with diabetes insipidus. A definite increase in the chloride U/P ratio occurred when the infusion was stopped.

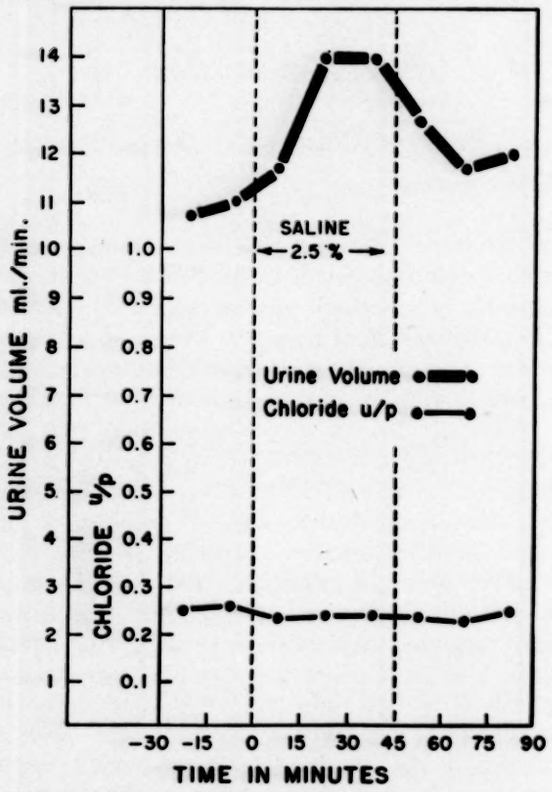

FIG. 1. Patient S. W. The effect of intravenous hypertonic sodium chloride solution on the rate of urine flow and chloride U/P ratio.

On another day the patient's response to the intramuscular injection of 5 units of pitressin was studied. The patient drank 200 ml. of tap water every thirty minutes throughout the test period. Urine collections were made at thirty-minute intervals, and after two control periods the patient was given pitressin. The results are shown in Figure 3. It should be noted that the time scale is one-half that of the other figure. It was assumed that the plasma chloride concentration would remain relatively constant during the period of the test, and therefore that changes in urine chloride concentration would reflect adequately changes in the chloride U/P ratio. It will be seen that the response to pitressin was similar in all respects to the response obtained by the Hickey-Hare test. The rate of water excretion decreased sharply, reaching a steady state within forty-five minutes after the pitressin injection. The urine chloride concentration increased about sixfold during this forty-five-minute period but following this and during the steady state of water excretion there was a marked increase in the urine chloride concentration. During the post-injection time period of 60 to 210 minutes the rate of water excretion remained below 0.5 ml./min. but the urine chloride concentration continued to increase, reaching a maximum value of 120.5 mEq./L., which is almost certainly in excess of the plasma chloride concentration, although we do not have data on the plasma chloride concentration at this time.

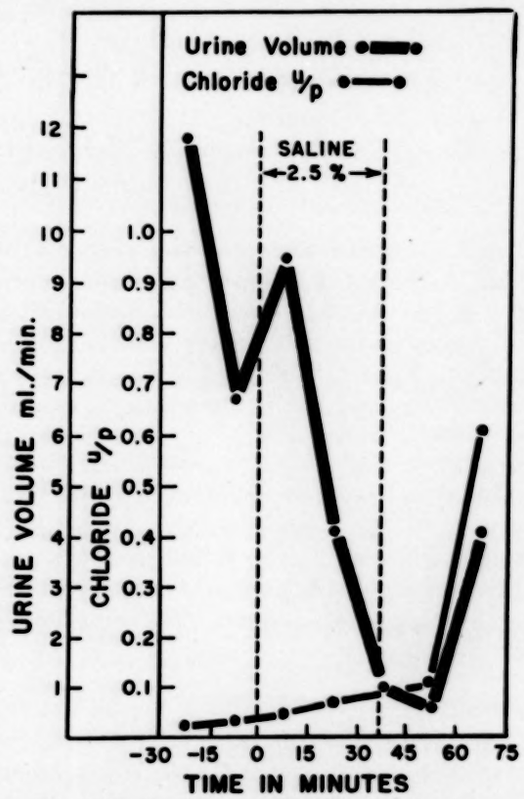

FIG. 2. Patient M. D. The effect of intravenous hypertonic sodium chloride solution on the rate of urine flow and chloride U/P ratio.

The average rate of chloride excretion during the control periods was 58 μEq./min. Following the pitressin injection this excretion rate decreased to a minimum value of 6 μEq./min. during the period 30 to 60 minutes after injec-

tion. Then the rate of chloride excretion began to increase, with fluctuations, and reached a maximum value of 124 μEq./min. (240 to 270 minutes after pitressin injection). At this time the rate of water excretion was 4.7 ml./min., or about one-half the control rate.

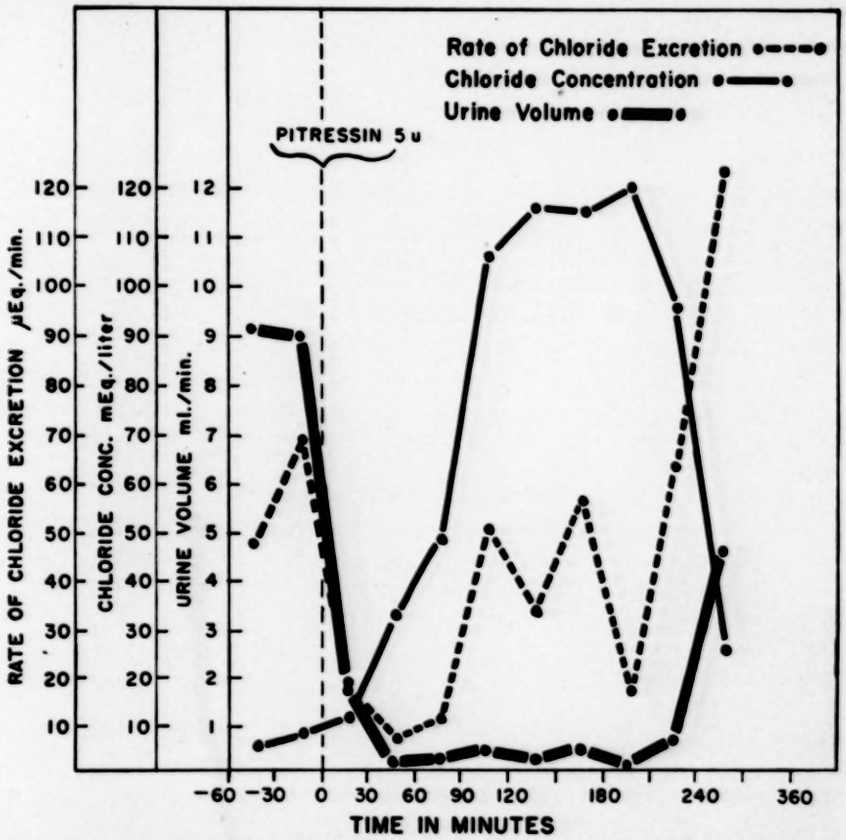

FIG. 3. Patient M. D. The effect of intramuscular pitressin (5 units) on the rate of urine flow, the rate of urinary chloride excretion and the urinary chloride concentration.

hypertonic saline solution, fails to increase the secretion of the antidiuretic hormone. In such situations the rate of urine flow does not decrease and there is little or no change in the chloride U/P.[1]

In a test of this type an increase in the chloride U/P ratio is a result of an increased urinary chloride concentration primarily, since the plasma chloride concentration changes slightly. Information concerning the control of chloride excretion is incomplete. Several mechanisms could cause an increase in the urinary chloride concentration: (1) the load of chloride presented to the tubule may exceed the tubular capacity for chloride reabsorption in the normal person but not in the patient with diabetes insipidus, (2) the reabsorption of water by the renal tubule, under the influence of the antidiuretic hormone, may exceed the reabsorption rate of chloride without invoking a specific effect on the chloride reabsorption rate or (3) the antidiuretic hormone, or some other substance liberated by the posterior pituitary

COMMENT

The Hickey-Hare test is based on the assumption that the infusion of a 2.5 per cent sodium chloride solution, by increasing the osmotic pressure of the plasma, constitutes an effective stimulus to activate the hypothalamic-hypophyseal mechanism in the normal individual. The result of this activation is an increase in the secretion of the antidiuretic hormone of the posterior pituitary gland. The increased antidiuretic hormone causes a marked decrease in the rate of urine formation and an increase in the ratio between the urinary chloride and plasma chloride concentrations (U/P). In the individual with dysfunction of the hypothalamic-hypophyseal mechanism, the stimulus, i.e., the

gland, may not only specifically increase the rate of water reabsorption but also may specifically decrease the reabsorption rate of chloride.

In considering possibility (1) available data in the literature were reëxamined. The tubular chloride load is a function of the plasma chloride concentration and the glomerular filtration rate (GFR). Typically the plasma chloride concentration in a patient with diabetes insipidus is within normal limits. There are few data describing the glomerular filtration rate in this condition, and the reports on the GFR in experimental diabetes insipidus are not consistent.[7] Hickey and Hare[1] have reported a decreased GFR in two patients with diabetes insipidus. These patients had a decreased tubular chloride load when compared to the normal person under similar experimental conditions. If under the conditions of the test the increased urinary chloride concentration in the normal, as opposed to the patient with diabetes insipidus, were simply a function of tubular chloride overloading in the normal without reaching the maximal tubular capacity in the patient with diabetes insipidus, the ratio of the load to the rate of chloride reabsorption should increase considerably in the normal while it would remain relatively unchanged in the patient with diabetes insipidus. Calculations were made for the ratio from the data of Hickey and Hare on three individuals and no significant difference was found. The normal's control ratio was 1.02 and this increased to 1.05 during the loading. The two patients with diabetes insipidus had control ratios of 1.02 and 1.00 respectively and these increased to 1.08 and 1.01 during the load. One must conclude that the difference in the chloride response to the test of the normal and the patient with diabetes insipidus cannot be explained on the basis of renal tubular chloride loads.

Possibility (2) would imply that the antidiuretic hormone specifically increases the reabsorptive rate for water without specifically affecting the chloride reabsorption. Studies by Murphy and Stead[4] and by Sinclair-Smith et al.[5] support this concept. The infusion of a 125–146 mM. solution of sodium chloride resulted in a water diuresis with a decreasing urinary chloride concentration[4] but after the infusion was stopped there was an abrupt decrease in the rate of urine flow and an increase in urinary chloride concentration with little or no change in the rate of chloride excretion, suggesting that the rate of chloride reabsorption was unaffected during the period of increased rate of water reabsorption. This antidiuresis is attributed to the release of antidiuretic hormone. Two of three normal hydrated subjects[5] showed a slight, but presumably non-significant, increase in the rate of chloride excretion following smoking or after the intravenous injection of 40 to 100 milli-units of pitressin, while the third subject showed a slightly decreased rate of excretion. All of these subjects had a marked decrease in the rate of urine flow. It was the conclusion of both of these groups of investigators that the antidiuretic hormone has no specific effect on chloride reabsorption.

The third possibility (3) states that the antidiuretic hormone or some substance liberated by the posterior pituitary gland and also present in extracts from the gland may not only specifically increase the rate of reabsorption of water by the tubule but also may specifically decrease the reabsorption rate of chloride by the tubule. Evidence obtained with experimental animals supports this hypothesis.[7] Using large intramuscular doses of pitressin (10 units), the effect on chloride excretion in the human was variable,[6] but in seven non-hydrated subjects and in nine hydrated subjects the injection of pitressin was followed by an increased urinary chloride concentration and an increased urinary chloride excretion without a simultaneous decrease in the rate of water excretion. These data suggest that some substance in the extract may inhibit specifically the reabsorption of chloride.

It is clear that the factors involved in the regulation of chloride excretion are poorly understood. It is also clear that the possible role of the posterior pituitary gland in this regulation may be complex. Evidence presented here (Figs. 2 and 3) as well as previously discussed evidence,[6] obtained during a steady state as far as the rate of water excretion is concerned, suggests that stimulation of the posterior pituitary by 2.5 per cent sodium chloride infusion or the injection of pitressin may have a specific effect on chloride excretion. It is possible that the difference in interpretation of the function of the posterior pituitary gland in the excretion of chloride may be due to quantitative or qualitative differences in the secretion of the gland under varying degrees of stimulation, to differences in the quantity of glandular extract used by various investigators, or to a temporal

difference in the effect which discloses a difference in the specific effects of the secretion. In a complex situation what one observes may be the resultant of the effects of several factors and therefore the effect of a single factor may be obscured. For this reason we emphasize that observation of the effect of the posterior pituitary on the excretion of chloride should be made during a steady state of water excretion.

Examination of the data on patient M. D. shows that there was a "normal" liberation of antidiuretic hormone by the stimulus of the 2.5 per cent sodium chloride infusion, since the rate of urine flow decreased abruptly. (Fig. 2.) However, during this time the reabsorption of chloride proceeded at approximately the same rate as the reabsorption of water since the chloride U/P did not increase. This is contrary to the normal response.[1,4] As the effect on water reabsorption began to decrease there was a sudden increase in the urinary chloride concentration. It is difficult to explain these observations without considering some specific influence of extrarenal origin on the tubular reabsorption of chloride. Since the injection of an extract of the posterior pituitary gland caused a similar effect on chloride excretion (Fig. 3), it is suggestive that the posterior pituitary gland is specifically involved in the regulation of chloride excretion.

The evidence suggests that patient M. D. had a functioning hypothalamic-hypophyseal mechanism as shown by the change in urine flow. However, the usual response of the urinary chloride concentration was delayed. In such instances of a paradoxical result the use of pitressin is of value in interpreting the Hickey-Hare test.

SUMMARY

In a patient with polyuria the results obtained with the Hickey-Hare test were consistent with a normally functioning hypothalamic-hypophyseal mechanism as far as the urine excretion rate was concerned but were not consistent with normal function with respect to the changes in the chloride U/P ratio. The patient responded in a similar manner to the injection of pitressin.

Some factors influencing the excretion of chloride and the relationship of the posterior pituitary gland to chloride regulation are discussed.

REFERENCES

1. Hickey, R. C. and Hare, K. The renal excretion of chloride and water in diabetes insipidus. *J. Clin. Investigation*, 23: 768, 1944.
2. Peters, J. P. and D. D. Van Slyke. Quantitative Clinical Chemistry. Baltimore, 1932. The Williams and Wilkins Co.
3. Van Slyke, D. D. and Hiller, Alma. Application of Sendroy's iodometric chloride titration to protein-containing fluids. *J. Biol. Chem.*, 167: 107, 1947.
4. Murphy, R. J. F. and Stead, E. A., Jr. Effects of exogenous posterior pituitary antidiuretic hormone on water and electrolyte excretion. *J. Clin. Investigation*, 30: 1055, 1951.
5. Sinclair-Smith, B. C., Sisson, J., Kattus, A. A., Genecin, A., Monge, C., McKeever, W. and Newman, E. V. The effects of posterior pituitary extract and smoking on water, sodium and chloride excretion in normal subjects and in patients with congestive failure. *Bull. Johns Hopkins Hosp.*, 87: 221, 1950.
6. Little, J. M., Wallace, S. L., Whatley, E. C. and Anderson, G. A. Effect of pitressin on the urinary excretion of chloride and water in the human. *Am. J. Physiol.*, 151: 174, 1947.
7. Smith, H. W. The Kidney. Structure and Function in Health and Disease. New York, 1951. Oxford University Press.

Temporal Arteritis*

A Critical Evaluation of This Disorder and a Report of Three Cases

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ALTHOUGH the original report by Horton and others in 1932 described a precise clinical and pathologic entity, characterized as a form of arteritis first noted in the temporal vessels, many subsequent articles have tended to obscure rather than to illuminate the nature of this disorder. Persons with this type of arterial inflammation have low grade fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and painful, tender areas over the scalp and along the course of the temporal arteries. The disease occurs practically without exception in elderly individuals, chiefly women. Generalized symptoms may include fatigue, faintness, vertigo, nausea and vomiting. Localized findings peculiar to the syndrome are headaches of great severity and tenderness with hyperesthesia over the temporal areas, associated with hot, swollen and tender temporal arteries. The headaches may be unilateral or bilateral, depending on whether one or both temporal arteries are involved. Painful mastication and pains in the neck, ears and upper cheeks are sometimes present. Ocular disturbances, which may accompany the headaches, include retrobulbar pain, blurring of vision and photophobia. Indeed, the condition may sometimes progress to complete blindness. Laboratory data usually show a microcytic anemia and mild leukocytosis without eosinophilia. Although most authors agree that the disease is self-limited and benign, with complete remission in a year's time or less, some cases apparently have terminated fatally.[2,3,9,13,14]

The etiology of temporal arteritis is not known. In general, the possible etiologic agents suggested have been an infectious incitant, hypersensitivity or perhaps a degenerative phenomenon of aging. Convincing or even plausible proof for any of these theories is lacking.

The reported pathologic changes in the affected arteries are typical. The lesion is segmental although in the involved regions the chronic inflammatory process extends into all layers of the arterial wall. The adventitia appears to be first affected and inflammatory cells, chiefly lymphocytes, neutrophils and occasional eosinophils, infiltrate widely, often revealing conspicuous perivascular cuffing about the vasa vasorum, which are greatly thickened and sometimes occluded. Patchy necrosis of the media is noted and granulomatous changes are observed, the latter characterized by the presence of foreign body giant cells of the Langhans type and proliferating fibrous tissue. The foreign body giant cells, incidentally, are so striking as to be one of the pathognomonic features of this disorder. Marked fibrous tissue proliferation of the intima so greatly thickens this coat that the lumen of the artery is often nearly obliterated. A thrombus sometimes is present to diminish further the size of the lumen.

Therapy is directed at interruption of sensory pain fibers. Thus excision of a segment of the vessel often results in complete disappearance of symptoms. Roberts and Askey[10] have recently reported four instances of a type of cranial arteritis in which perivascular infiltration of procaine produced marked relief. Whether these were cases of true temporal arteritis is not made clear, as biopsy specimens were not obtained.

CASE 1. A sixty-seven year old white man entered the hospital because of severe left temporal headache, of four months' duration, which was severe, intermittent and aggravated by physical and nervous tension. A month prior to admission, pain and headaches in the opposite temporal region and blurring of vision in the left eye had developed. Night sweats, malaise, anorexia and a 20 pound loss of weight were also present. The patient also had extensive rectal

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fistulas. The past history, family history and social history were not significant.

The patient was a well developed and moderately well nourished man with marked paralysis agitans present for twenty years. The temporal arteries could be felt as firm, thickened, pulseless, moderately tender cords. Over the left temporal region there was marked hyperesthesia. Except for exquisite rectal tenderness little else of note was found.

The hemoglobin was 13.0 gm., the red cell count 4.8 million and the white cell count 9,700 with 76 per cent neutrophils, 22 per cent lymphocytes and 2 per cent eosinophils. The urine was normal. Gastrointestinal series, barium enema and chest roentgenograms were negative. A stool specimen was negative for occult blood. Blood cultures and agglutination tests for typhoid fever, brucellosis and typhus were negative.

The hospital course was characterized by daily afternoon elevations of temperature to 100°F. and frequent episodes of headache, worse on the left and associated with blurring of vision of both eyes. An operation was performed for repair of the rectal fistulas. At the same time a 2 cm. segment of the left temporal artery was excised. Immediately following excision of this segment complete and immediate disappearance of the headaches and of the blurring of vision on the left occurred. Infiltration by 2 per cent procaine hydrochloride of the right temporal artery produced similar results. However, pain recurred in the right temporal region. Because of the recurrence of pain, benadryl,® 50 mg. three times daily, was prescribed, and the pain has been absent since the beginning of this antihistaminic regimen.

Pathologically the specimen removed at operation consisted of a segment of the left temporal artery approximately 2.0 cm. in length. Microscopically it showed marked thickening of all layers of the vessel with extreme narrowing of the lumen which did not contain a thrombus. (Fig. 1.) The intima was thickened by inflamed proliferating fibrous tissue and by acellular, hyaline connective tissue, presumably collagen. There was no evidence of atheroma formation. The media was the site of a diffuse granulomatous lesion characterized by the presence of foreign body giant cells, some of which were similar to those of the Langhans type, marked necrosis in the smooth muscle and elastic tissues, and irregular fibroblastic proliferation. (Figs. 2 and 3.) A diffuse but irregular infiltration of lymphocytes was present and a rare neutrophil was seen. The adventitia was thickened by dense fibrous tissue and the walls of the vasa vasorum were also thickened and showed slight cellular hyperplasia and hyaline intimal thickening. Their lumens were small.

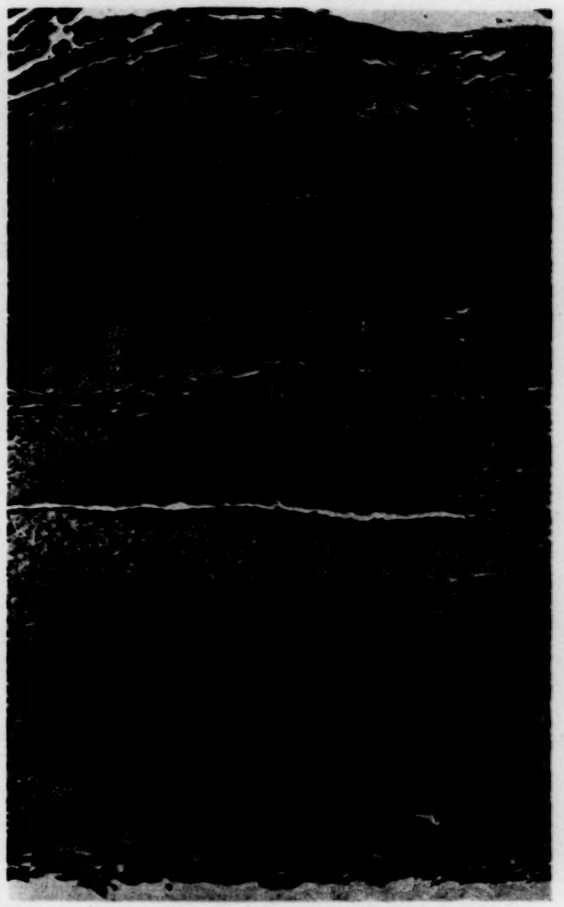

FIG. 1. Case I. Tangential section of temporal artery; there is thickening of all layers of this vessel by inflamed fibrous tissue. A narrow zone of necrosis bordered by inflamed granulation tissue may be seen in the media. Foreign body giant cells are barely discernible adjacent to the necrotic foci. The lumen remains as a thin slit. No thrombus is present, however; × 100.

CASE II. A seventy year old white woman entered the hospital because of fever, headache, nausea and vomiting. The headaches began approximately one year before admission and were localized in the frontal areas bilaterally. Two and a half months before admission she had first noted the onset of soreness in the right temporal region. At this time she observed that the temporal vessels had become unduly prominent and tortuous. Intermittent elevations in

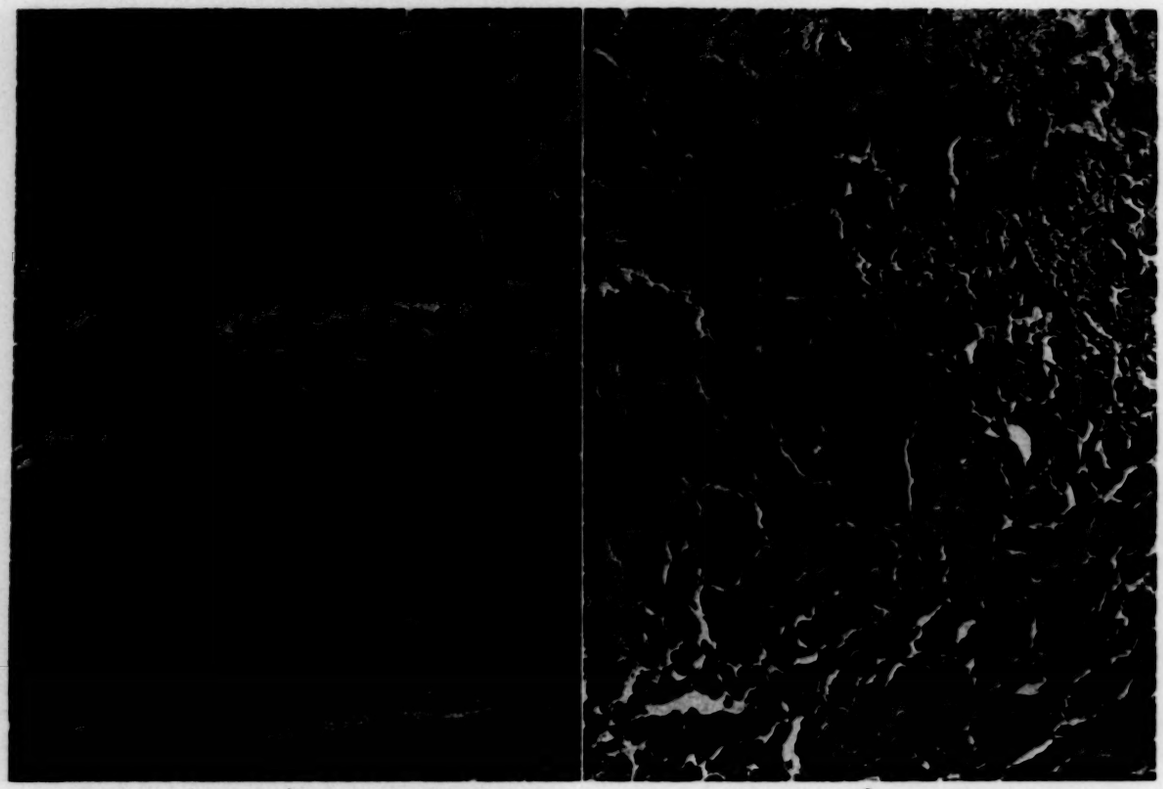

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FIG. 2. The same vessel under greater magnification; the necrotic tissues of the media, with the adjacent inflamed vascularized granulation tissue, are more readily seen and the granulomatous character of the inflammation is obvious. Giant cells of foreign body type lie peripheral to the necrotic region. Fibrous thickening of the intima, due to actual fibrous proliferation and not to atherosclerosis, is evident. The tissue is lightly infiltrated by lymphocytes. A few thin-walled vascular channels lined by endothelium are also to be noted in the intima; × 225.

FIG. 3. The same lesion showing a foreign body giant cell; the granulomatous inflammation of temporal arteritis is typified by the presence of giant cells of the foreign body type. The nuclei of these cells tend to form a ring about an acellular eosinophilic hyaline core and often resemble giant cells of the Langhans type. This cell is adjacent to the region of necrosis in the media; × 625.

temperature to as high as 102°F. were associated with these developments. Two weeks before admission the patient had had a bout of nausea and vomiting and had developed loss of vision for which she was hospitalized elsewhere. At that time she had received penicillin and sulfonamide therapy. During the two-week interim before hospitalization she had noted that the pain radiated from the temporal region to the front of the ear and below the chin. She also had associated loss of appetite, color, strength and weight. The past history, family history and system review were not significant.

Physical examination on admission to the Albany Hospital revealed a well preserved white woman complaining of severe headache and slightly tender temporal vessels. The temporal arteries were relatively firm although they were found to pulsate slightly when palpated. Daily afternoon temperature elevations to approximately 101°F. were observed.

The red cell count was 3.3 million and the white cell count 6,700 with a normal differential. Sedimentation rate was 50 mm. per hour. The fasting blood sugar was 86 mg. per cent and the non-protein nitrogen 27 mg. per cent. The Wassermann test was negative. The urine was normal. X-ray films of the chest and skull as well as a gastrointestinal series and a flat plate of the abdomen were all negative. Agglutination tests for brucellosis and typhoid were negative. Blood, stool and urine culture yielded only contaminants.

A section of the right temporal artery was removed for biopsy and the pathologic changes were those of typical temporal arteritis. Following the removal of this segment the pain disappeared on that side. The patient continued to

have nausea, vomiting and pain on the opposite side, and a segment of this temporal vessel was likewise removed, and was also found to have undergone the typical granulomatous changes of temporal arteritis. Following this operation the patient became free of headaches and visual difficulties.

Case III. This patient was a seventy-one year old white man admitted to the Albany Hospital because of wrist drop and severe headache, both of a few weeks' duration. The headache occurred in the left frontal region, was constantly present but of varying severity, and was associated with diminished visual acuity of the left eye. The patient's other symptoms included episodes of sudden loss of consciousness and falling without convulsions. The family history, past history and personal history bore no relation to the present disease. On physical examination the significant findings were present in the temporal arteries, which were firm, beaded and slightly tender. The eyes on neurologic examination showed marked impairment of vision on the left with only questionable light perception in the nasal field remaining, fixation of the pupil to light and changes in the optic disc which were suggestive of papilledema and optic neuritis. The right wrist showed wrist drop and the left foot slight atrophy; there was also diminished sensation over the right wrist and hand as well as the left foot. Slight right facial weakness was present. It was at first thought that the patient had multiple vitamin deficiencies, resulting in polyneuritis and multiple small cerebrovascular accidents.

Lumbar puncture revealed normal cerebrospinal fluid pressure and 90 mg. per cent of protein. The colloidal gold curve was third zone or meningitic in type. The hemoglobin was 11 gm.; the red cell count 3.1 million and the white cell count 7,500 with 56 neutrophils, 3 eosinophils, 4 basophils, 36 lymphocytes and 1 monocyte. The Wassermann test was negative. The fasting blood sugar was 83 mg. per cent, non-protein nitrogen 31 mg. per cent, cholesterol 189 mg. per cent with 66 per cent cholesterol ester. Total blood protein was 6.3 gm. with 3.7 gm. of albumin and 2.6 gm. of globulin. The 1 minute serum bilirubin was 0.15 mg. per cent; thirty minutes, 0.8 mg. per cent. Bromsulfalein test revealed 12.6 per cent of the dye remaining in the blood at forty-five minutes. Evidence of healed tuberculosis and an enlarged tortuous aorta was noted in a chest roentgenogram. The electrocardiogram gave evidence of generalized myocardial damage. A BMR test was normal. An angiogram of the left internal carotid artery was unsuccessful as no opaque material was visible in the vascular system of the brain.

Twice during his hospital course the patient had an elevated temperature of 99°F. together with frequent episodes of loss of consciousness and with continuing pain in both temporal regions. A biopsy of a 2.0 cm. segment of the posterior branch of the right temporal artery was performed after the patient had been in the hospital approximately one month. The lumen of this vessel was reduced to little more than a narrow slit. The various layers of the artery were difficult to identify as these structures had been virtually replaced by chronic granulomatous tissue in which occasional foreign body giant cells of the Langhans type were present. There was no evidence of thrombosis.

The patient lapsed into coma on the thirty-fourth hospital day and died. An autopsy was performed and the findings are summarized briefly since a detailed report of the extent and nature of the granulomatous arterial lesions will be the subject of another report. There was advanced atherosclerosis of both internal carotid arteries with, in addition, the changes of granulomatous arteritis with foreign body giant cell reaction. A recanalized thrombus was present at the site of granulomatous inflammation in one of the arteries but the thrombus in the other carotid artery was not situated at the site of granulomatous inflammation. The thrombi in both of these vessels had virtually obliterated already narrowed lumens, and widespread concomitant encephalomalacia of the left frontoparietal region of the left cerebral hemisphere was present.

The changes in the carotid arteries, while essentially similar to the typical granulomatous lesions of temporal arteries, were different in some respects. The intima of these vessels showed the changes of atherosclerosis, chiefly hyaline thickening and degeneration, rather than the proliferation of fibroblasts usually seen. The lumens of the carotid arteries, while appreciably narrowed, were not the mere slits that are often found. So advanced were the arteriosclerotic lesions in these vessels that it was thought that the thrombi might be due to arteriosclerosis rather than the granulomatous inflammation of temporal arteritis.

Several of the small intracerebral vessels

showed suggestive, although not typical, granulomatous changes. Careful examination of the arteries of the other internal viscera, including the heart and kidneys, failed to reveal granulomatous changes although advanced arteriosclerosis was present.

COMMENTS

Soon after temporal arteritis was reported as a new and unusual clinical entity, the suggestion was made that it might represent merely a variant of periarteritis nodosa. However, its relatively benign course differed sharply from that of periarteritis nodosa and the facts that individuals over the age of fifty-five seemed to be affected and that the lesions were generally limited to the cranial arteries seemed to set it apart from this other serious and widespread arterial disease. Actually this disorder appears to represent a distinct clinicopathologic entity, the etiology of which is as yet obscure. The paper by Kilbourne and Wolff[6] has clearly delineated its significant clinical aspects while others[9,14] have given a detailed description of the significant pathologic changes. The most striking change is the presence of a foreign body giant cell reaction so characterized that it has been suggested that this lesion be called granulomatous arteritis of undetermined cause or, better, non-specific granulomatous arteritis.[8]

It should be pointed out that many authors have noted shortcomings in the term temporal arteritis and many synonyms such as cranial arteritis and arteritis of Horton and Magath have been suggested. None of these has gained currency. Certainly one serious defect should not be lost sight of in the term temporal arteritis. The term as originally used was not an all-inclusive phrase designed to encompass every inflammatory lesion of the temporal artery. It was conceived to be and should still be considered as a definite clinicopathologic entity, the histopathologic changes of which are quite specific. In the case of Kilbourne and Wolff[6] the clinical aspects of the disorder were classic. Unfortunately, however, the pathologic report of the excised artery in their case described an inflammatory lesion in which there was no mention of a granulomatous or foreign body giant cell type of reaction. On the basis of this report and others, in which the arterial inflammatory changes were non-specific; cases have been reported of inflammatory lesions of the temporal arteries which not only were not granulomatous but also had none of the clinical features associated with this disorder. For example, a case of cranial arteritis in a young woman twenty-two years of age was reported.[4] Despite a normal leukocyte count, the absence of a recorded red blood cell count and the presence of a pulsating temporal artery which did not show granulomatous lesions in the media, this case was considered to be an example of the disorder described by Horton and Magath. Certainly not all inflammatory lesions of the temporal artery are granulomatous and the inclusion of all kinds of inflammatory lesions of this vessel as examples of temporal arteritis as described by Horton and Magath would seem to be unwarranted. On the other hand, it seems valid to assume that granulomatous arteritis of arteries other than the temporal, when the lesions exhibit the same type of pathologic change as that seen in temporal arteritis, represents a manifestation of the same fundamental disorder.[11,12]

It should be noted in this connection that inflammatory lesions of arteries are not rare although autopsy and surgical specimens of most of these vessels are not often obtained. The temporal artery, however, is ideal for surgical extirpation because of its easy accessibility. This same factor, accessibility, may in fact make this vessel more vulnerable to various inflammatory or degenerative disorders. Thus care should be taken to classify accurately the changes one finds in these vessels. Possibly in older persons arteries less readily accessible to biopsy or autopsy may undergo the granulomatous changes noted most frequently in the temporal arteries.

If a definite etiologic factor could be demonstrated, one might then be less concerned about strict adherence to pathologic criteria. However, in the absence of a proved etiologic agent it seems reasonable to insist that only biopsied cases showing the characteristic granulomatous lesions in the affected artery can be considered at this time to comprise the entity so clearly described by Horton and Magath.

Although the undesirability of the term temporal arteritis is well recognized, an acceptable substitute apparently has not been proposed. We believe that a term emphasizing the pathologic aspects of this disorder rather than any regional distribution would be most desirable since this lesion has been found in such diverse locations as the radial and coronary arteries. Consequently the term non-specific

granulomatous arteritis or, more simply, granulomatous arteritis seems appropriate.

SUMMARY

A brief clinical and pathologic summary of the syndrome of temporal arteritis is made, with a report of three new cases, one of which was fatal and in which an autopsy was performed. This condition, first reported in 1932 by Horton, Magath and Brown, is characterized by severe headaches, pain in the temporal region and the presence of inflamed, thickened and tortuous temporal arteries. Constitutional symptoms of a generalized infection are also present.

The characteristic pathologic lesion consists of proliferation of inflamed fibrous tissue of all layers of the affected vessel, together with focal necrosis and granulomatous lesions associated with foreign body giant cell formation in the media. Good therapeutic results are obtained by procaine injection, surgical excision of a portion of the diseased vessel and, in at least one instance, antihistaminic therapy. The disorder is usually self-limited and non-fatal. Although generally a localized vascular disease of the temporal arteries, other cranial arteries, as well as arteries in other parts of the body, may show the same type of lesion.

We believe the term temporal arteritis should be restricted to instances in which the affected vessel has undergone the characteristic granulomatous change associated with foreign body giant cells. We also suggest changing the regional designation temporal arteritis to that of a pathologic entity, such as non-specific granulomatous arteritis or, more simply, granulomatous arteritis.

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REFERENCES

1. Horton, B. T., Magath, T. B. and Brown, G. E. An undescribed form of arteritis of the temporal vessels. *Proc. Staff. Meet., Mayo Clin.*, 7: 700, 1932.
2. Hoyt, L. H., Perera, G. A. and Kauvas, A. J. Temporal arteritis. *New England J. Med.*, 225: 283, 1941.
3. Murphy, J. R. The syndrome of temporal arteritis. *New York State J. Med.*, 42: 2236, 1942.
4. Meyers, L. and Lord, L. W. Cranial arteritis. *J. A. M. A.*, 138: 169, 1948.
5. Shannon, E. W. and Solomon, J. Bilateral temporal arteritis with complete loss of vision. *J. A. M. A.*, 127: 647, 1945.
6. Kilbourne, E. D. and Wolff, H. G. Cranial arteritis: a critical evaluation of the syndrome of temporal arteritis with report of case. *Ann. Int. Med.*, 24: 1, 1946.
7. Chasnoff, J. and Vorzimer, J. J. Temporal arteritis: a local manifestation of a systemic disease. *Ann. Int. Med.*, 20: 327, 1944.
8. Dantes, D. A. Temporal arteritis. *J. A. M. A.*, 131: 1265, 1946.
9. Dick, G. F. and Freeman, G. Temporal arteritis *J. A. M. A.*, 114: 645, 1940.
10. Roberts, A. M. and Askey, J. M. Temporal arteritis. *J. A. M. A.*, 137: 697, 1948.
11. Gilmour, J. R. Giant-cell chronic arteritis. *J. Path. & Bact.*, 83: 263, 1941.
12. Sproul, E. E. A case of temporal arteritis. *New York State J. Med.*, 42: 345, 1942.
13. Horton, B. T. and Magath, T. B. Arteritis of the temporal vessels: report of seven cases. *Proc. Staff Meet., Mayo Clin.*, 12: 548, 1937.
14. Scott, T. and Maxwell, E. S. Temporal arteritis: a case report. *Internat. Clin.*, 2: 220, 1941.
15. Bowers, J. M. Arteritis of the temporal vessels. *Arch. Int. Med.*, 66: 384, 1940.

Review

The Effects and Treatment of Nerve Gas Poisoning*

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THE nerve gases are a group of organic esters of phosphoric acid derivatives which, because of their volatility and toxicity, are among the most potent of the known chemical warfare agents.[1] They are also the most adaptable to long range attack, as upon civilian populations.[2] The majority of the compounds comprising this group were synthesized by the Germans before and during the recent war, and one of them was stored in large quantities for military use, although never actually employed in combat. Some of the German installations for the production and study of nerve gases were located in what is now the eastern zone of Germany.

A number of organic esters of phosphoric acid derivatives, which are related to the nerve gases but are somewhat less toxic, have proved to be useful in medicine and in agriculture. These compounds, like the nerve gases, owe their activity to their ability to inhibit cholinesterase (ChE) enzymes more or less irreversibly, with resultant cholinergic effects attributable to the accumulation of acetylcholine in the effector organs. Di-isopropyl fluorophosphate (DFP) has been employed to study the role of ChE enzymes in normal function and in disease,[3] and as a therapeutic agent in the management of abdominal distention,[3] urinary retention and glaucoma.[4] Tetraethyl pyrophosphate (TEPP) has proved to be of value in the management of some patients with myasthenia gravis.[5] Parathion, hexaethyl tetraphosphate (HETP) and TEPP have been widely used throughout the world as insecticides and their indiscriminate dispersal has resulted in a number of instances of fatal exposure.[6-8]

The mechanism of action, effects, prevention and treatment of nerve gas poisoning have proved to be similar in general to those of the more familiar organic phosphate anticholinesterase (antiChE) compounds. The present report will attempt to summarize the effects that have been observed in normal volunteer subjects following the administration of, or exposure to, one of the more toxic of these nerve gases. This compound, which is of considerable military importance, will be referred to as "nerve gas." It is probable that the effects of other nerve gases will prove to be similar, differing mainly in dose-effect relationship. Because of security considerations detailed information concerning the chemical composition and physical properties of "nerve gas," and the quantitative aspects of dose-effect relationship have been omitted from this report.

EFFECTS OF "NERVE GAS" IN MAN

"Nerve gas" is a colorless liquid which is volatile at ordinary temperatures. Its effects, like those of the other organic phosphate antiChE compounds, are referable to the inhibition of ChE enzymes in the tissues and the resultant accumulation of acetylcholine at the ends of postganglionic cholinergic nerves to smooth and cardiac muscle and secretory glands (muscarine-like effects), preganglionic nerves to autonomic ganglia and motor nerves to striated muscle (nicotine-like effects), and in the central nervous system. The inhibition of ChE enzymes by "nerve gas" rapidly becomes irreversible, so that the effects of this compound are prolonged. Until the tissue cholinesterases have been restored to normal activity, probably by the regeneration of enzyme over a period of days or weeks, subjects who have been exposed to "nerve gas" have increased susceptibility to its action, which may be cumulative.

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ABSORPTION

"Nerve gas," like the other organic phosphate anticholinesterases, may be absorbed by any route. When dispersed as a vapor, spray or aerosol, or adsorbed on dust, it is readily absorbed through the respiratory tract and conjunctivas. Liquid "nerve gas," or solutions, may be absorbed through the skin, conjunctivas, gastrointestinal tract, or following injection.

LOCAL OCULAR AND RESPIRATORY EFFECTS (TABLE I)

Conjunctival exposure to, or inhalation of, "nerve gas" produces local cholinergic effects which are attributable to the inhibition of ChE enzymes in the eye and in the upper and lower respiratory tract. These occur before there is any evidence of systemic absorption. The ocular effects consist of miosis, a sensation of "pressure" in and behind the eye, frontal headache and conjunctival hyperemia. The pupillary constriction may be unequal. Severe local exposure produces maximal miosis and eye pain, especially on focussing. Vision is usually not grossly impaired, although there may be slight dimness especially in the peripheral fields. Occasionally there is nausea and vomiting which, in the absence of systemic absorption, has been attributed to a reflex initiated by the ocular effects. The local effects of "nerve gas" on the respiratory tract consist of rhinorrhea, nasal hyperemia, a sensation of tightness in the chest and occasionally prolonged wheezing expiration, suggestive of bronchoconstriction or increased bronchial secretion. It is possible that exposure to high concentrations may produce more marked evidence of bronchoconstriction.

SYSTEMIC EFFECTS (TABLE I)

These may follow absorption of "nerve gas" by any route. Absorption through the skin or gastrointestinal tract produces no local irritant change so that exposure by these routes may go undetected until symptoms begin. "Nerve gas" has no taste and no distinctive odor.

Muscarine-like effects: These are usually the first to appear. The earliest manifestations are usually anorexia, nausea, sweating, epigastric and substernal "tightness" (probably due to cardiospasm) with "heartburn" and eructation, and "tightness" in the chest. The sequence of these symptoms may vary with the route of exposure, gastrointestinal effects usually being the earliest following ingestion, sweating (and at times localized muscular fasciculations) following percutaneous exposure, and respiratory effects following inhalation. If absorption is sufficiently great, whether due to a single exposure or to repeated smaller exposures, the initial effects are followed by abdominal cramps, increased peristalsis, vomiting, profuse sweating and dyspnea, with reduction in vital capacity and in maximal breathing capacity. In some but not all subjects the dyspnea is accompanied with varying degrees of audible wheezing, with prolonged expiration, and by spirometric evidence of reduction in the vital capacity and in the rate of movement of air into and out of the lungs suggestive of bronchoconstriction or increased bronchial secretion. Respiratory manifestations are more marked when the respiratory tract is the route of absorption and when the subject is in the older age group or has a history of antecedent respiratory disease. They would be expected to be most marked in asthmatic subjects. Respiratory as well as gastrointestinal symptoms may increase following the smoking of one or two cigarettes. Extensive exposure also results in diarrhea, tenesmus, increased salivation and lacrimation, pallor, slight miosis, urinary frequency and occasionally slight bradycardia and pain referred to the lower thoracic cage. More severe muscarine-like effects of "nerve gas" have not yet been observed in man. Following accidental exposure to sublethal or lethal amounts of parathion the symptoms outlined previously have been followed by involuntary defecation and urination, excessive bronchial secretion and occasionally by pulmonary edema.[6] Severe bronchoconstriction has not been observed in man following lethal exposure to parathion but has been observed in experimental animals after sublethal or lethal exposure to either parathion or "nerve gas."

Nicotine-like effects: Shortly after the onset of moderate muscarine-like effects there ensue increased fatigability, mild generalized weakness which is increased by exertion, involuntary muscular twitching, scattered fasciculations and sometimes muscle cramps. Extensive exposure results in severe generalized weakness, including weakness of the muscles of respiration with respiratory distress. The fasciculations, which usually appear first in the eyelids and in the facial and calf muscles, become generalized. Electromyographic studies show alterations in neuromuscular function which are attributable

TABLE 1

Site of Action	Signs and Symptoms	
	A*	B†
Following Local Exposure		
1. *Muscarine-like*		
Pupils	Miosis, marked or maximal, occasionally unequal	
Ciliary body	Frontal headache, eye pain on focussing, slight dimness of vision, occasional nausea and vomiting	
Conjunctivas	Hyperemia	
Nasal mucous membranes	Rhinorrhea, hyperemia	
Bronchial tree	Tightness in chest, occasionally with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion	
Following Systemic Absorption		
Gastrointestinal	Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (? cardiospasm) with "heartburn" and eructation, diarrhea, tenesmus	Involuntary defecation
Sweat glands	Increased sweating	
Salivary glands	Increased salivation	
Lacrimal glands	Increased lacrimation	
Heart	Slight bradycardia	
Bronchial tree	Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnea, slight pain in chest	Increased bronchial secretion, pulmonary edema, with cyanosis
Pupils	Slight miosis, occasionally unequal	Maximal miosis (pin-point, non-reactive)
Ciliary body		Blurring of vision
Bladder	Frequency	Involuntary micturition
2. *Nicotine-like*		
Striated muscle	Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalized weakness, including muscles of respiration, with dyspnea	
Sympathetic ganglia	Pallor, occasional elevation of blood pressure	
3. *Central Nervous System*	Giddiness, excessive dreaming, insomnia, nightmares, tension, anxiety, jitteriness, restlessness, emotional lability, headache, tremor, withdrawal and depression, reduction of voltage of EEG, bursts of slow waves of elevated voltage in EEG, especially on overventilation, drowsiness, difficulty concentrating, slowness of recall, confusion	Paresthesias, slurred speech, ataxia, generalized weakness, coma, with absence of reflexes, Cheyne-Stokes respirations, convulsions, depression of respiratory and circulatory centers

* Signs and symptoms that followed local exposure to and systemic absorption of "nerve gas." Gastrointestinal, pulmonary, nicotine-like and central nervous system symptoms are listed in order of appearance.

† Additional signs and symptoms that followed accidental absorption of sub-lethal or lethal amounts of TEPP or parathion and which would be expected to follow absorption of proportionate amounts of "nerve gas."

to the accumulation of excessive acetylcholine at the motor end plate. (Fig. 1.) Occasionally mild or moderate elevation of blood pressure occurs, probably owing to stimulation of sympathetic ganglia.

Central nervous system effects: Tension, anxiety, jitteriness, restlessness, emotional lability and giddiness occur early, followed by insomnia, with excessive dreaming and occasionally nightmares. If the exposure is extensive, headache, tremor, drowsiness, difficulty in concentrating, slowness of recall and mental confusion develop. In some subjects there is withdrawal and depression. Following asymptomatic exposure there is no change in the electroencephalogram. With the appearance of mild symptoms there is usually a slight diminution in potential and, when moderate symptoms are present, irregularities in rhythm, variation and increase in potential, and intermittent bursts of abnormal waves similar to those seen in patients with epilepsy appear. These consist of slow waves (2½ to 6 per second) of elevated voltage (70 to 150 mv.), usually most marked in the frontal leads. They usually are not striking prior to overventilation, appearing in intermittent bursts after one or more minutes of overventilation. (Fig. 2.) More severe central neural effects of "nerve gas" have not been studied in man. Following accidental sublethal or lethal exposure to parathion the aforementioned symptoms have been followed by ataxia, changes in speech consisting of slurring, difficulty in forming words and multiple repetition of the last syllable, coma, areflexia, Cheyne-Stokes respiration, generalized convulsions and, finally, depression of respiration.[6]

ONSET AND DURATION OF SYMPTOMS

Local effects begin within a few minutes after exposure. The local symptoms last for several hours to a day, while the miosis persists for two to five days. Moderate systemic effects begin within half an hour after respiratory exposure, three-quarters of an hour after oral exposure, and two to three hours after percutaneous exposure. It is probable that the latent period following exposure to sublethal or lethal concentrations would be shorter. Mild systemic symptoms may last for a few hours while moderately severe symptoms may not reach their maximum severity until four to eight hours after onset, and usually diminish over a period of one to six days. During the period of recovery symptoms may recur intermittently, especially following exertion. The electroencephalographic changes may persist for as long as eleven to eighteen days.

The time interval between exposure to "nerve gas" and death is not known in man. The average time interval between accidental exposure to parathion and death has been ten and a half hours, and between the onset of symptoms and death nine hours. Following overwhelming exposure to parathion, especially by inhalation, these time intervals have been as short as one hour. Terminally, respiration has become shallow, labored and rapid, cyanosis has ensued, and the blood pressure has then become unobtainable.[6] Factors contributing to death due to parathion are believed to be depression of the respiratory and circulatory centers in the brain, weakness of the muscles of respiration due to neuromuscular block, and, in some instances, excessive bronchial secretion, pulmonary edema and bronchoconstriction. It is likely that death due to "nerve gas" would be the result of similar functional alterations. Postmortem examination following death due to parathion has usually revealed capillary dilatation, hyperemia and edema of the lungs, sometimes of the brain as well, and occasionally of all the organs.[6]

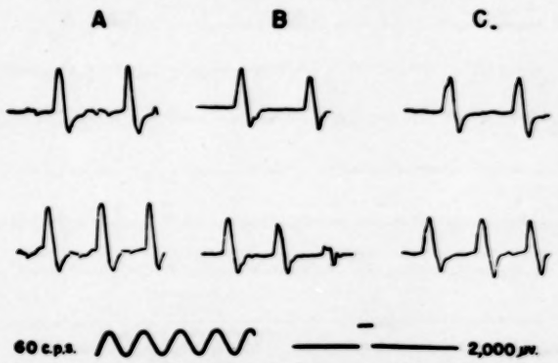

FIG. 1. The effect of percutaneous absorption (left forearm) of a solution of "nerve gas" on the muscle action potential (right adductor digiti quinti) of a normal subject in response to supramaximal stimulation of the right ulnar nerve. A, before exposure; B, sixty-five hours after sufficient exposure to produce moderately severe generalized weakness and abnormal fatigability. At this time mild symptoms were still present. The electromyogram reveals a normal response to the initial stimulus, slight depression of the response to the second stimulus and marked depression of the response to the third. The response to subsequent stimuli delivered at similar intervals was also reduced. C, eighty-nine hours after exposure. Symptoms had almost disappeared, and the response to repetitive stimuli was near normal.

CUMULATIVE EFFECTS OF REPEATED EXPOSURE

Daily exposure to concentrations of "nerve gas" which are insufficient to produce symptoms following a single exposure may result in the onset of symptoms after several days. Continued daily exposure may be followed by increasingly severe effects. After symptoms subside, increased susceptibility persists for one or more days. The degree of exposure required to produce recurrence of symptoms and the severity of these symptoms depend on the extent of and time interval since the last exposure. The exact duration of the period of increased susceptibility to "nerve gas" is not known. Following subsidence of symptoms produced by the related compound, DFP, increased susceptibility to antiChE compound administration persisted for one to three weeks.[3] Increased susceptibility is not limited to the antiChE agent that is initially absorbed but would be expected to apply to any other antiChE or direct acting cholinergic compound.

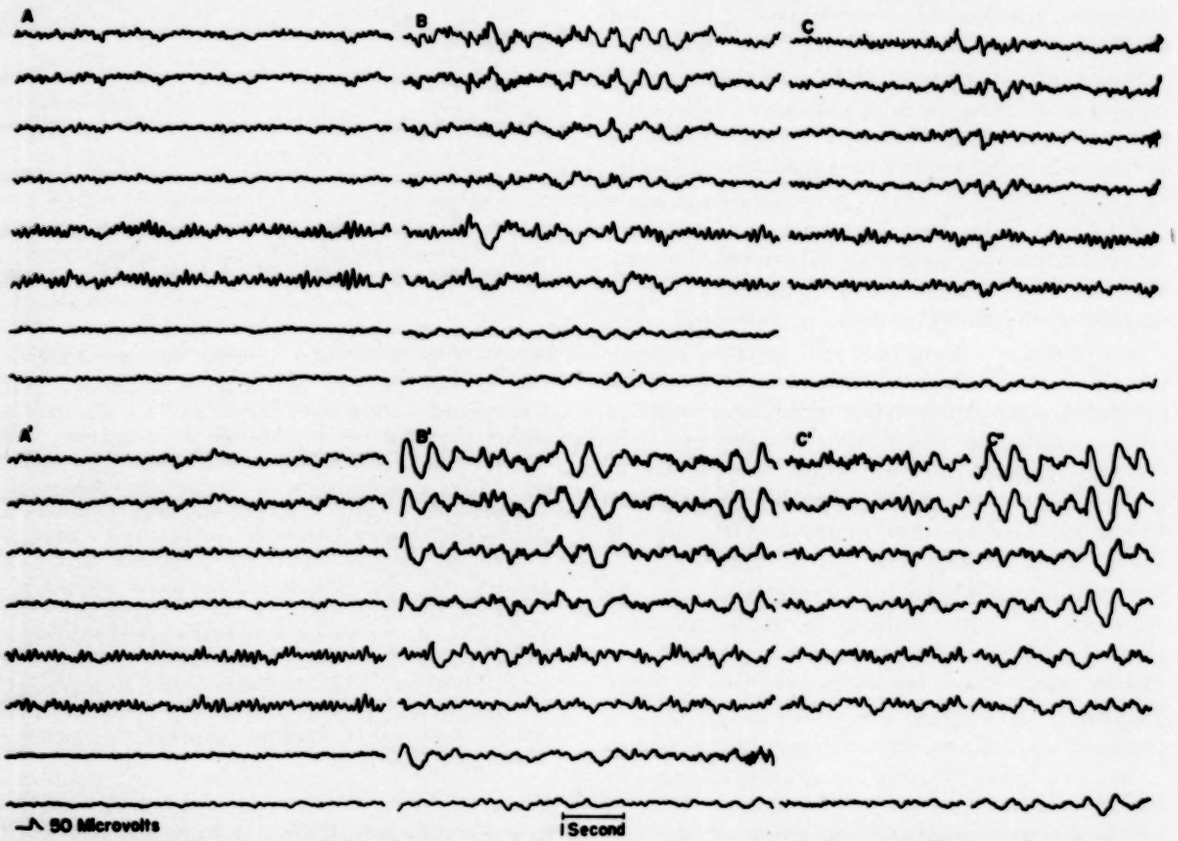

FIG. 2. The effect of oral administration of a solution of "nerve gas" on the electroencephalogram of a normal subject. Alterations have been brought out by hyperventilation. A and A′, controls before administration and after three and five minutes of hyperventilation. B and B′, following administration of "nerve gas" and after three and four minutes of hyperventilation. The degree of abnormality increased progressively during the period of hyperventilation. C, C′ and C″, fifteen minutes after B′, and five to ten minutes after the intravenous injection of 1 mg. atropine sulfate. C is after three minutes of hyperventilation, C′ after four minutes and C″ after five minutes. The injection of atropine has resulted in reduction in potential and in irregularities of rhythm and potential (C and C′) and has delayed the appearance of abnormal slow waves of increased potential. These did not appear until after five minutes of hyperventilation (C″).

EFFECT ON PLASMA AND RED BLOOD CELL CHOLINESTERASE ACTIVITY

The signs and symptoms produced by "nerve gas" are due to inhibition of the ChE enzymes of the nervous system, muscle and secretory glands, and not to the coincident inhibition of ChE enzymes of the plasma and red blood cells. However, since it is not possible to determine the ChE activity of the tissues in man during life, it is necessary to rely on the ChE activity of the plasma and red blood cells as a guide of

some value in detecting systemic absorption of "nerve gas" and persistence of its effects.

Effect of a single exposure: The systemic absorption of "nerve gas" by any route is followed by a decrease in plasma and red blood cell ChE activity. (Fig. 3.) The maximum depression of ChE activity occurs within one to two hours after exposure. The degree of depression of the ChE activity of the red blood cells is slightly greater than that of the plasma, corresponding to the relative sensitivity of these enzymes to "nerve gas" *in vitro*. The degree of depression of plasma and red blood cell ChE varies with the amount of "nerve gas" absorbed, the logarithm of the fraction of enzyme inhibited being proportional to the amount of agent absorbed.

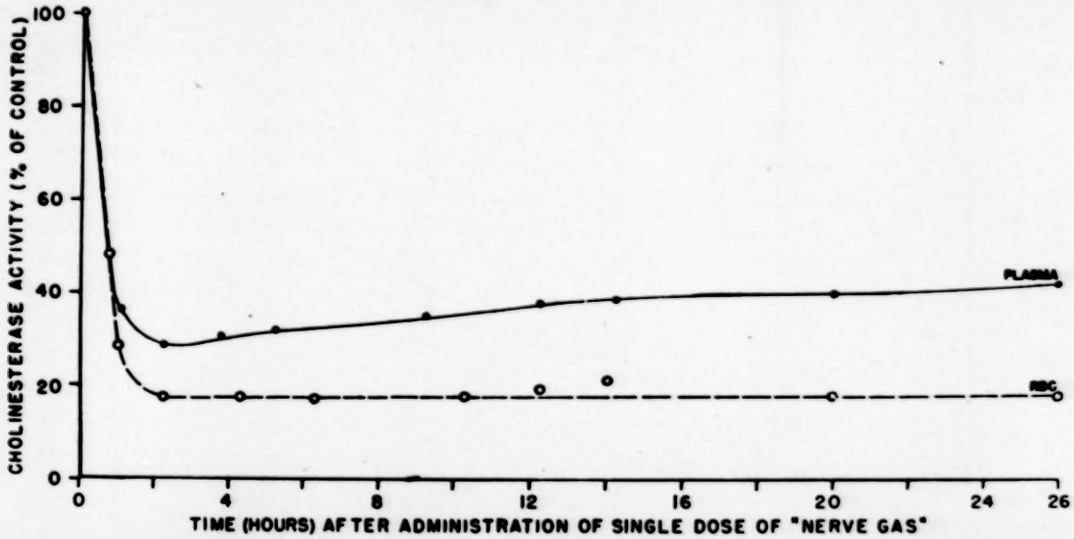

FIG. 3. Depression of ChE activity (plasma ●— — —●, and red blood cell 0— — —0) after administration to a normal subject of a single oral dose of a solution of "nerve gas," and restoration during the first day. ChE activity was determined both manometrically[9] and by electrometric measurement of change in hydrogen ion concentration.[10]

Restoration of plasma and red blood cell ChE activity (Figure 4): Restoration of the former begins three to ten hours after cessation of exposure, and of the latter twenty-four to forty-eight hours after exposure. Plasma ChE activity increases by about 13 per cent of original activity during the first day after exposure, about 8 per cent on the second day, 6 per cent on the third, 5 per cent on the fourth, and 2 to 4 per cent per day on subsequent days until return to the original level of activity. This requires thirty to forty days following marked depression of activity. The red blood cell ChE activity increases more slowly at a regular rate of approximately 1 per cent of original activity per day. After nearly complete depression of red blood cell ChE, ninety to 100 days are required for restoration of the original activity. Once restoration of plasma and red blood cell ChE activity has begun, the rates are independent of the amount of "nerve gas" that has been absorbed, the time of exposure, and the degree of depression of ChE activity at the end of the exposure. The available evidence indicates that plasma ChE is regenerated by the liver and that the restoration of red blood cell ChE reflects the rate of replacement of red blood cells.[3]

Effect of repeated exposure on plasma and red blood cell ChE activity: Repeated exposure at intervals of hours or days results in progressive depression of ChE activity. (Fig. 5.) The logarithm of the fraction of plasma or red blood cell ChE inhibited at any time is proportional to the amount of agent absorbed and is independent of the level of ChE activity. If the intervals between exposures are long enough for some restoration of plasma ChE activity to occur, but not of red blood cell ChE, the latter is depressed more rapidly. If there is insufficient time for the restoration of red blood cell ChE activity between exposures, the effect on this enzyme is almost entirely cumulative and it may be almost completely inactivated. Under these circumstances the logarithm of the decrease in red blood cell ChE activity at any time is proportional to the total amount of "nerve gas" that has been absorbed up to that time.

Relation of the effects of "nerve gas" to the plasma and red blood cell ChE activity: Following exposure to "nerve gas" the plasma and red blood cell ChE activity may be depressed considerably below normal before the appearance of signs or symptoms. The level of ChE activity at which symptoms begin after a single exposure varies with the route of absorption and is highest when absorption is rapid. Following a single intravascular (intra-arterial) injection systemic symptoms may begin when the plasma and red blood cell ChE are at approximately 60 and 50 per cent of initial activity; following oral exposure, at 35 and 25 per cent; and following percutaneous exposure, at 15 and 10 per cent. The corresponding depression of tissue ChE activity is not known. Brain and muscle ChE enzymes of man have the same sensitivity to inhibition by "nerve gas" *in vitro* as red blood cell ChE. It is possible that the tissue ChE activity may approximate that of the red blood cells after a single intravascular injection but may be inhibited to a lesser degree when "nerve gas" is absorbed more slowly, allowing more protracted "buffering" action by plasma and red blood cell ChE. It also appears likely that the rate of inactivation of tissue ChE enzymes may influence the level of tissue ChE activity at which symptoms begin.

Following repeated exposure to "nerve gas" there is no predictable correlation between the onset of symptoms and the precise level of ChE activity of the plasma or red blood cells. The ChE activity of the red blood cells may be gradually depressed to near zero by repeated exposure over a period of several days without systemic symptoms necessarily ensuing, or without any relation to the severity of symptoms that occur. The red blood cell ChE remains at a low level of activity long after the disappearance of symptoms, indicating that the ChE activity of the tissues is restored more rapidly than that of the red blood cells, although the rate of restoration is not known. It is probable that this restoration occurs over a period of several days, since symptoms of "nerve gas" poisoning may last as long as six days and electroencephalographic changes eighteen days, and since there is increased susceptibility to a subsequent exposure for one or more days after the cessation of symptoms.

The restoration of plasma ChE activity may be increased by the intravenous administration of plasma or whole blood, and red blood cell ChE activity by whole blood, but this does not affect the symptoms of "nerve gas" intoxication or appreciably reduce the susceptibility to further exposure. The administration of plasma

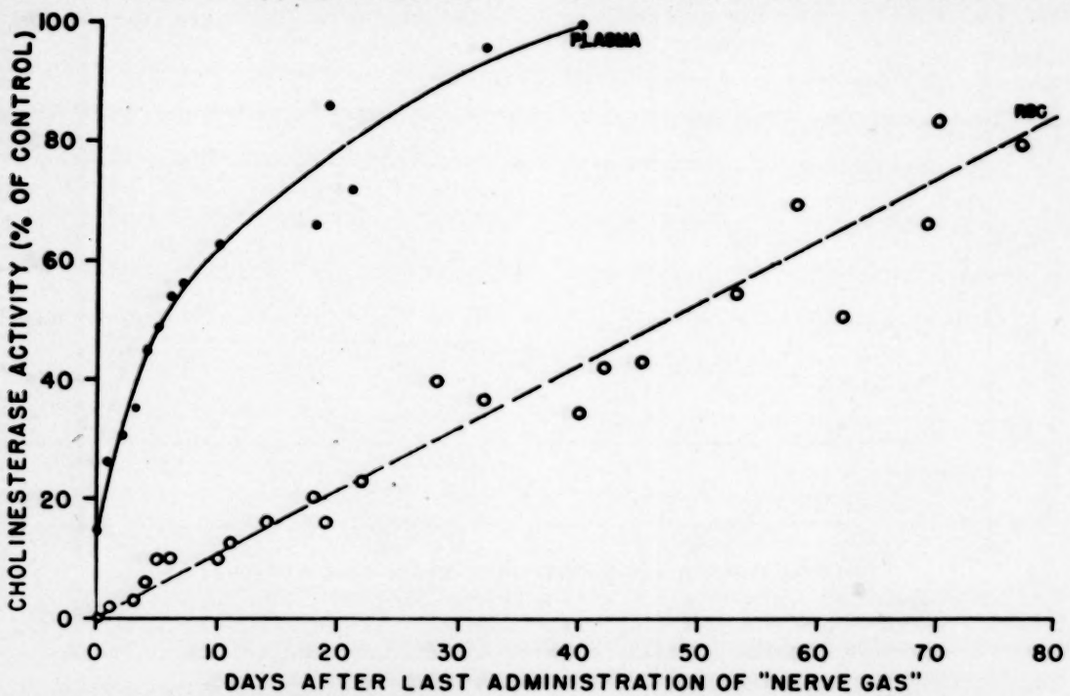

FIG. 4. Rate of restoration of ChE activity (plasma ●———●, and red blood cell 0———0) after cessation of "nerve gas" administration. Average values obtained in ten normal subjects are recorded.

or blood probably has no effect on the ChE activity of the tissues. While an increase in plasma and red blood cell ChE activity may, to some extent, act as a "buffer" against subsequent exposure to "nerve gas," this appears to be much less important than the degree of depression of tissue ChE enzymes at the time of the exposure.

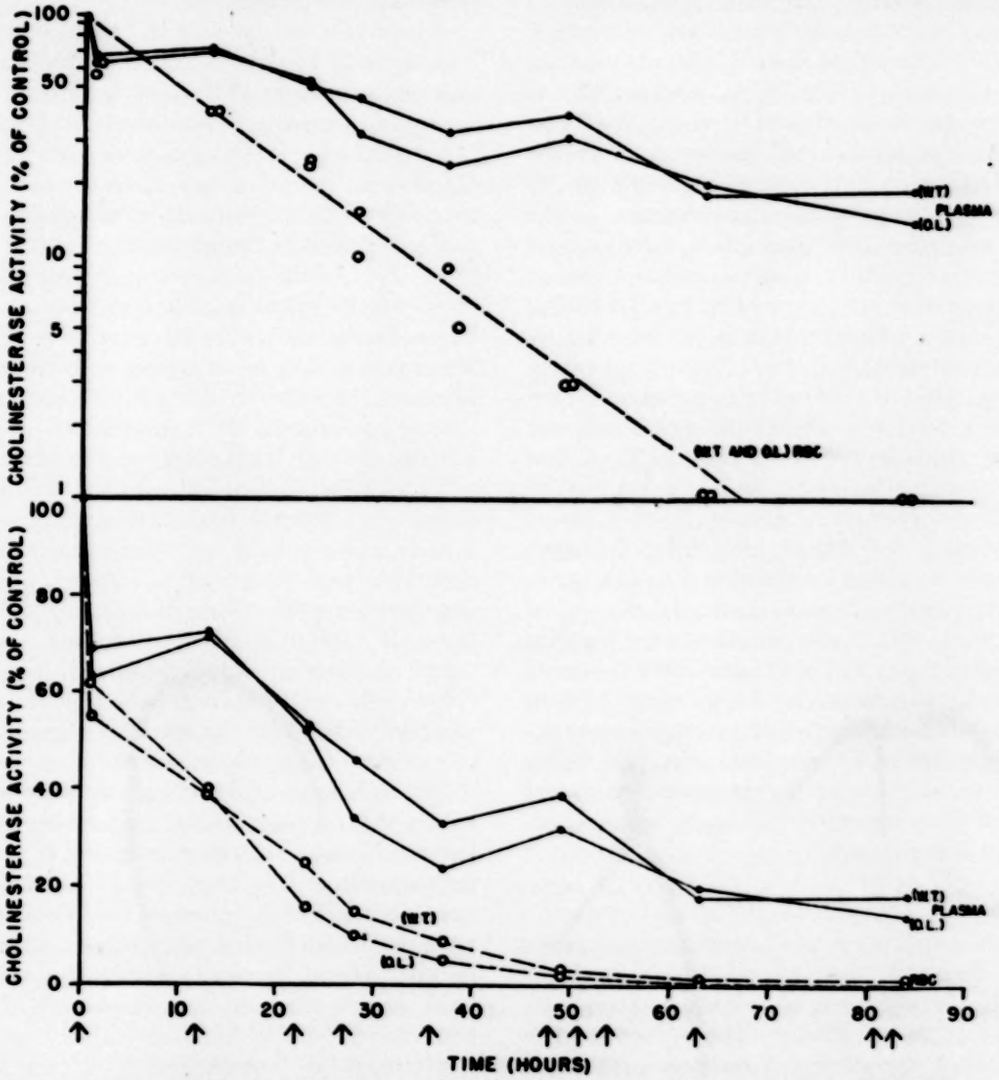

FIG. 5. *Lower graph:* Effect of the repeated oral administration of "nerve gas" on ChE activity (plasma ●———●, and red blood cell 0———0) of two normal subjects (W. T. and O. L.) Each arrow represents the oral administration of a solution of "nerve gas." *Upper graph:* Same as lower graph, except that ChE activity is plotted on logarithmic scale.

RELATION OF THE EFFECTS OF "NERVE GAS" TO THE CHOLINESTERASE ACTIVITY OF THE TISSUES

Observations following the administration of DFP and TEPP to patients with myasthenia gravis,[9] and following accidental exposure to lethal amounts of parathion,[6] indicate that these compounds exert their effects by depressing the ChE activity of the tissues below a threshold at which changes in function begin. "Nerve gas" appears to act in the same way. It is very likely that any of these antiChE compounds may reduce the ChE activity of the tissues considerably without the appearance of any warning systemic symptoms, while a further reduction below the level compatible with normal function may result in the appearance of symptoms, and a greater reduction in death. The difference between the doses of these compounds that produce systemic symptoms and the doses that

would probably be lethal is not very great, suggesting that there is not a wide range between the threshold of tissue ChE activity at which symptoms begin and the level below which fatal functional alterations occur.

The onset and severity of symptoms due to "nerve gas" appear to be related not only to the degree of inhibition of tissue ChE enzymes but also to the rates of inhibition, irreversible inactivation and restoration of these enzymes, and to the rate of removal of "nerve gas" by the body. The removal of "nerve gas" appears to be by combination with ChE enzymes in the blood and tissues and with other proteins, and by hydrolysis, which is catalyzed in various tissues, especially the liver. Little is known of other means of detoxification of this compound, or of its excretion, but these do not appear to play an important part in the removal of "nerve gas" from the body. If it is assumed that red blood cell, muscle and brain cholinesterases are equally sensitive to inhibition by "nerve gas" *in vivo* after intravascular injection, as they are *in vitro*, the sites and degree of uptake of "nerve gas" in the body can be computed from the observed depression of plasma and red blood cell ChE activity. Such computation suggests that almost all of intravascularly administered "nerve gas" can be accounted for by its reaction with ChE enzymes and adjacent proteins, approximately three-fourths reacting with voluntary muscle, one-fifth with plasma and red blood cells, and the remainder with brain, spinal cord, liver and other tissues.

OTHER EFFECTS OF "NERVE GAS"

Exposure to "nerve gas" produces no known effects other than inhibition of ChE enzymes of the blood and tissues, and signs and symptoms attributable to the latter. There is no other alteration of the chemical constituents of the blood, no alteration of the formed elements of the blood and no change in the urine or in renal or hepatic function. Recovery from moderate intoxication due to "nerve gas" has always been complete. When recovery from very severe intoxication due to parathion has occurred, it has also been complete,[6] but it is likely that there may be residual effects if convulsions or anoxia are sufficiently prolonged.

PREVENTION OF "NERVE GAS" POISONING

Since "nerve gas" may be absorbed by any route, numerous precautions must be taken to prevent or reduce the degree of absorption in the event of a gas attack or of accidental exposure. Because of the progressive and cumulative effects of this compound the prevention of further absorption is particularly urgent once symptoms have begun.

(1) In case of exposure to vapor or aerosol of "nerve gas," gas masks which provide oronasal and ocular protection should be put on at once and worn as long as chemical test procedures indicate the presence of "nerve gas" in the air. Casualties should have masks applied and properly adjusted. Wind dispersal to unprotected subjects should be anticipated.

(2) In case of cutaneous exposure to liquid "nerve gas" splash the skin should be washed immediately with copious quantities of water. If the skin is dirty or oily, soap and water should be used. If water is not available, the liquid "nerve gas" should be gently blotted away. The skin should *not* be rubbed or abraded, as this will increase absorption. Breaks in the skin should be covered with adhesive tape before anticipated exposure, as more rapid absorption occurs through broken skin. Liquid "nerve gas" penetrates rapidly through clothing and slowly through rubber gloves and aprons. Contaminated clothing should be removed at once and rubber gloves and aprons, even though of heavy material, should be changed after several hours of exposure to the liquid agent.

(3) In case of conjunctival exposure to liquid splash the conjunctivae should be immediately irrigated with copious quantities of water or isotonic saline.

(4) In case of ingestion of food or water contaminated with "nerve gas" gastric lavage should be carried out as soon as possible. Water and food supplies which are suspected of recent contamination should be examined for "nerve gas" prior to consumption. Water supplies should be decontaminated if necessary. Contaminated food should be discarded or the outer layers removed and the residue examined prior to use.

(5) Material contaminated with liquid "nerve gas" should be thoroughly washed with as concentrated a solution of alkali as is practicable, or else buried or burned.

(6) Aid stations for the observation and treatment of casualties should be established upwind from any contaminated area. Contaminated clothing should be removed by personnel wearing heavy rubber gloves and aprons, gas masks

and, if possible, protective coveralls, before casualties are received in the aid station. Members of decontaminating squads should also wear rubber boots and protective hoods.

(7) Subjects who are suspected of having absorbed toxic amounts of "nerve gas" should be removed from further exposure and observed for several hours. If the degree of absorption is believed to have been such as to endanger life, atropine may be administered before symptoms begin, in doses of 2 mg. orally or intramuscularly, repeated at intervals of one to four hours in an effort to maintain a mild degree of atropinization. This should be followed by observation for at least twenty-four hours, since the onset of symptoms may be delayed by atropine. Atropine should *not* be administered for preventive purposes *prior* to contemplated exposure to "nerve gas," as this may increase respiratory absorption of "nerve gas" by inhibiting bronchoconstriction and bronchial secretion.

(8) Systemic absorption of "nerve gas" may be detected by symptoms, if these ensue, or by depression of plasma *and* red blood cell ChE activity, which can be determined by a simple chemical procedure.[10] Plasma ChE activity may be reduced by the absorption of antiChE compounds or by many acute or chronic illnesses, particularly those affecting hepatic function, while red blood cell ChE may be reduced only by antiChE compounds or by relatively uncommon blood dyscrasias, such as pernicious anemia or leukemia.[3] Subjects who have absorbed "nerve gas" should, if possible, avoid subsequent exposure until the plasma and red blood cell cholinesterases have returned to near normal activity. This will usually require several weeks.

TREATMENT OF SYMPTOMS DUE TO "NERVE GAS"

The following recommendations for treatment of "nerve gas" poisoning are based largely upon experience acquired in the management of moderate symptoms due to "nerve gas," and of severe intoxication following administration of TEPP[5] or accidental exposure to parathion.[6]

Treatment relies chiefly on atropine which has a moderate inhibitory effect on the muscarine-like manifestations, a mild to moderate effect on the central nervous system manifestations, including the electroencephalographic changes (Figure 2), and no influence on the nicotine-like manifestations at the neuromuscular junction. Patients who have symptoms due to systemic absorption of "nerve gas" have increased tolerance for atropine so that fairly large doses may be administered before signs of atropinization appear. The absence of increased tolerance for atropine would indicate that "nerve gas" intoxication is probably either not present or is mild.

Mild or moderate symptoms due to "nerve gas" are treated by the intramuscular administration of 2 mg. of atropine sulfate or tartrate. The effects of intramuscular atropine begin about twenty minutes after injection and are maximal forty minutes after injection. If the muscarine-like symptoms of "nerve gas" are not relieved, and if signs of atropinization (dry mouth and skin) do not appear, the injection of atropine should be repeated at thirty-minute intervals until this occurs. A mild degree of atropinization should then be maintained for at least twenty-four hours by the oral or intramuscular administration of 1 or 2 mg. of atropine at intervals of one to four hours. Smoking should be avoided until the symptoms of "nerve gas" intoxication have subsided.

Severe symptoms should be treated by the intravenous administration of 2 to 4 mg. of atropine. The effects of intravenous atropine begin one to four minutes after injection and are maximal within eight minutes after injection. If the muscarine-like symptoms are not relieved, and if signs of atropinization do not appear, the intravenous injection of atropine in doses of 2 mg. should be repeated at five- to ten-minute intervals until this occurs. A mild degree of atropinization should then be maintained for at least forty-eight hours.

Ocular symptoms produced by the local absorption of "nerve gas" do not respond to the systemic administration of atropine but are relieved by the local instillation of 2 per cent homatropine, repeated as needed at intervals of several hours for one to three days. Severe symptoms may require the local instillation of 0.5 or 1 per cent atropine. If local ocular effects of "nerve gas" are present, the size of the pupil cannot be used as an indicator of the systemic effects of "nerve gas" or of atropine.

Respiratory depression due to "nerve gas" requires prompt artificial respiration. This is best performed by means of a portable bellows-type resuscitator, equipped with gas mask canister, but if this is not available manual artificial respiration should be instituted. The

Holger-Nielson method is the most efficient manual procedure. The subject, wearing a properly adjusted gas mask, lies prone with the head turned to one side, the neck hyperextended and the hands under the head. Inspiration is aided by raising the elbows upward and forward, and expiration by releasing the arms and applying pressure to the thorax near the lower border of the scapulas. These movements are repeated from ten to twelve times a minute. If atropine administration was not instituted prior to the onset of respiratory depression, this should be started simultaneously with artificial respiration. Oxygen should be given, if available, and oropheryngeal suction and airway employed, if necessary. In the most severe intoxication artificial respiration may have to be maintained for hours.

If convulsions are prolonged, interfere with respiration and are not relieved by intravenous atropine, the careful administration of trimethadione (tridione), a barbiturate, or ether for their amelioration may be of value. Trimethadione may be given intravenously or intramuscularly, in doses of 1 gm., repeated if necessary. It has less depressant effect on respiration than the barbiturates. Morphine should not be administered.

SYMPTOMS DUE TO ATROPINE

The administration of a single dose of 2 mg. of atropine by any route to a subject who has absorbed little or no "nerve gas" produces mild symptoms, including dryness of the mouth and pharynx, with slight difficulty in swallowing, subjective warmth, slight tachycardia, some hesitancy of urination, and occasional desire to eructate. The pupils may be dilated but they react to light. In some subjects there may be mild drowsiness, slowness of memory and recall, subjective slowing of motor activity and blurring of near vision, particularly after intravenous administration of atropine. These symptoms should not interfere with ordinary activity. More severe symptoms are likely to occur if atropine is administered repeatedly to a subject who has absorbed little or no "nerve gas" or following overtreatment of a subject with mild symptoms. In the presence of severe anticholinesterase poisoning as much as 24 mg. of atropine may be administered in a day without producing symptoms attributable to atropine.

Overatropinization is recognized by the development of very dry mouth, thirst, hoarseness, dry flushed skin, dilated pupils, blurring of near vision, tachycardia (up to 140 per minute), urinary retention, constipation, slowing of mental and physical activity, restlessness, headache, disorientation, hallucinations, maniacal behavior and increasing drowsiness. Abnormal behavior may require restraint and, rarely, sedation. Overatropinization may be incapacitating but presents little danger to life. A single dose of as much as 10 mg. of atropine has been inadvertently administered intravenously to normal adults without endangering life, even in the absence of any prior absorption of "nerve gas," although it has, of course, produced very marked signs of overdose.

SUMMARY

The mechanism of action, effects, prevention and treatment of "nerve gas" poisoning are in general similar to those of the more familiar organic phosphate anticholinesterase compounds, such as DFP, TEPP and parathion. "Nerve gas" may be absorbed by any route. It produces local ocular and respiratory effects, and systemic effects, attributable to inhibition of cholinesterase enzymes in the smooth muscle of the eyes and respiratory and gastrointestinal tracts, and in the secretory glands, voluntary muscle and central nervous system. These effects are prolonged and cumulative. "Nerve gas" also produces concomitant inhibition of cholinesterase enzymes of the plasma and red blood cells, which rapidly becomes irreversible, following which enzyme activity is restored at rates compatible with regeneration of enzyme. Prevention of "nerve gas" poisoning following exposure relies upon the gas mask, protective clothing, the removal of cutaneous or conjunctival splash by means of water, and gastric lavage if necessary. Treatment is by the parenteral administration of atropine (to which there is increased tolerance), in repeated doses sufficient to maintain a mild degree of atropinization, by artificial respiration and oxygen if needed, and by the injection of trimethadione *if* convulsions interfere with respiration and are not relieved by atropine.

Acknowledgment. The observations that have been summarized on the effects of oral, percutaneous, intravascular and conjunctival exposure to "nerve gas," on alterations in ChE activity and on treatment with atropine were carried out under a contract between the Chemical Corps, U. S. Army, and the Johns

Hopkins University. The observations on the effects of oral administration were performed in collaboration with Dr. John C. Harvey and will be reported in greater detail at a later date. Studies on inhalation of "nerve gas" will be reported separately by Dr. Harvey and his collaborators.

Miss Barbara Ziegler, Miss Grace Saltzer and Mr. George I. Johnston rendered valuable technical assistance in this work. A particular debt of gratitude is due the volunteer subjects, without whose fine cooperation this study would not have been possible.

REFERENCES

1. Wood, J. R. Medical problems in chemical warfare. *J. A. M. A.*, 144: 606–609, 1950.
2. Wood, J. R. Chemical defense. *J. A. M. A.*, 145: 1264–1267, 1951.
3. Grob, D., Lilienthal, J. L., Jr., Harvey, A. M., Jones, B. F., Langworthy, O. R. and Talbot, S. A. The administration of di-isopropyl fluorophosphate (DFP) to man. I–IV. Effect on cholinesterase; systemic effects; effect on intestinal motility, central nervous system, and myasthenia gravis. *Bull. Johns Hopkins Hosp.*, 81: 217–292, 1947.
4. Leopold, I. H. and Comroe, J. H., Jr. Use of di-isopropyl fluorophosphate ("DFP") in treatment of glaucoma. *Arch. Ophth.*, 36: 1–16, 1946.
5. Grob, D. and Harvey, A. M. Observations on the effects of tetraethyl pyrophosphate (TEPP) in man and on its use in the treatment of myasthenia gravis. *Bull. Johns Hopkins Hosp.*, 84: 543–567, 1949.
6. Grob, D., Garlick, W. L. and Harvey, A. M. The toxic effects in man of the anticholinesterase insecticide parathion (p-nitrophenyl diethyl thionophosphate). *Bull. Johns Hopkins Hosp.*, 87: 106–129, 1950.
7. Pharmacology and toxicology of certain organic phosphorus insecticides. Report to the Council on Pharmacy and Chemistry of the American Medical Association. *J. A. M. A.*, 144: 104–108, 1950.
8. Grob, D. Uses and hazards of the organic phosphate anticholinesterase compounds. *Ann. Int. Med.*, 32: 1229–1234, 1950.
9. Grob, D., and Harvey, A. M. Cholinesterase activity of the tissues of man determined post mortem: "normal" values in infants and adults, and values in liver disease, myasthenia gravis, and after exposure to anticholinesterase compounds. Quart. Progress Report to Chemical Corps Medical Laboratories, Oct. 1, 1949.
10. Michel, H. O. An electrometric method for the determination of red blood cell and plasma cholinesterase activity. *J. Lab. & Clin. Med.*, 34: 1564–1568, 1949.

Seminars on Blood Coagulation

Mechanism of Blood Coagulation in Normal and Pathologic Conditions*

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THE role of vascular factors in physiologic hemostasis and in the pathogenesis of hemorrhagic diseases has been discussed in recent publications.[1–3] The present review will therefore, be limited to the blood coagulation phase of the hemostatic process. (Fig. 1.)

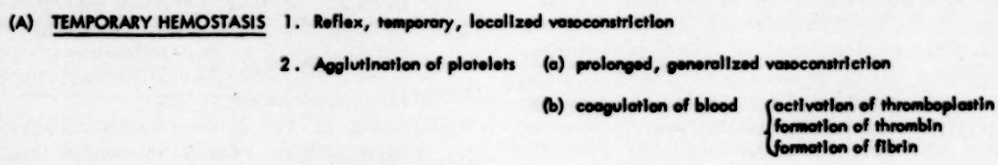

FIG. 1. Phases of hemostasis in man following vascular injury. The scheme emphasizes the prominent role of platelets in the process of hemostasis. Platelets (*a*) supply a vasoconstricting agent (? serotonin); (*b*) initiate the process of blood coagulation by supplying an agent indispensable for the activation of thromboplastin; (*c*) determine the retraction of the clot.

In this field there is a crying need for a unified terminology and a critical evaluation of all theories in the light of established facts. A discussion of this controversial subject may be useful to the clinician who wishes to find in the prevailing physiologic concepts guidance for the diagnosis and management of the bleeding patient.

INDIVIDUAL FACTORS WHICH TAKE PART IN THE PROCESS OF BLOOD COAGULATION

Factors which play a recognized role in the process of blood coagulation have been found in platelets, plasma and serum. (Table 1.) The properties of many of these factors and their mechanisms of action have been fairly well characterized.

Platelets have assumed an increasingly significant role in the process of hemostasis and blood coagulation. (Fig. 1.) They supply agents active in every phase of the clotting process: (1) *platelet thromboplastic factor*, which is indispensable for the activation of thromboplastin from an inactive plasma precursor (plasma thromboplastic factor or thromboplastinogen); (2) *platelet factor 1*, which accelerates the conversion of prothrombin to thrombin, and is probably closely related to the "serum accelerator"; (3) *platelet factor 2*, which accelerates the

$$\text{fibrinogen} \xrightarrow{\text{thrombin}} \text{fibrin reaction};$$

(4) *platelet factor 3* opposes the activity of heparin. It is likely that platelet thromboplastic factor and platelet factor *3* are in effect the same agent.[4] Increased heparin-like activity has been found in the plasma of patients with thrombocytopenia. Results obtained by means of heparin-protamine titration curves[5] have been interpreted as indicating an increase of heparin in the circulating plasma, but may be attributed only to the delay in coagulation due to lack of platelets and, possibly, deficiency of platelet factor *3*. The properties of the various platelet

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† Established Investigator, American Heart Association. The original work quoted in this review was performed during the tenure of a Damon Runyon Senior Clinical Research Fellowship, administered by the American Cancer Society, New York.

factors, together with technics for crude isolation, are presented in Table II and Figure 2.

Platelets also supply additional factors of no less importance in the process of hemostasis. Intact platelets are needed for clot retraction; this might be dependent upon the activity of a specific platelet component found in the hyalomere.[6] Agglutination and lysis of platelets which follow discontinuity of the vascular wall and a lesion of the intima cause release of a powerful vasoconstrictor (serotonin?). Bleeding time and probably capillary fragility appear related to platelet function. The importance of platelets in the process of hemostasis is indicated by the complex defect observed in thrombocytopenia, in which increased capillary fragility, prolonged bleeding time, delayed one-stage prothrombin time of plasma (due to deficiency of platelet factors *1* and *2*), reduced utilization of prothrombin during clotting (deficiency of platelet thromboplastic factor), increased sensitivity to heparin *in vitro* and *in vivo* (deficiency of platelet factor *3*) are found. The multiple functions of platelets in the hemostatic process are therefore possibly due to independent chemical constituents. This is suggested not only by the biochemical studies cited but also by observations conducted in patients with "thrombocytoasthenia," a bleeding tendency in which the number of platelets is normal although they appear abnormal in size, appearance and staining properties of the chromomere and hyalomere. In these patients one or more of the hemostatic functions may be abnormal (Table III), the most common occurrences being impaired clot retraction, defective utilization of prothrombin during clotting or prolonged bleeding time, singly or combined. These

TABLE I

WHERE THE VARIOUS COAGULATION FACTORS ARE FOUND

a) *Platelets*
1. Platelet thromboplastic factor
2. Platelet accelerator 1 (factor 1)
3. Platelet accelerator 2 (factor 2)
4. Platelet factor 3 (anti-heparin factor)

(b) *Plasma*

Factors favoring the coagulation of blood:
1. Plasma thromboplastic factor (thromboplastinogen, antihemophilic globulin)
2. Plasma thromboplastic component (PTC)
3. Prothrombin
4. Calcium
5. "Labile component" (labile factor, proaccelerin, plasma Ac-globulin)
6. "Stable component" (proconvertin, factor VII)
7. Fibrinogen

Factors opposing blood coagulation or taking part in the destruction of the formed clot:
8. Antithromboplastin
9. Antithrombin
10. Albumin X (heparin co-factor)
11. Profibrinolysin
12. Antifibrinolysin
13. Antifibrinolysokinase (fibrinokinase inhibitor)

(c) *Serum*
1. All factors found in plasma (with the exception of fibrinogen), in concentrations directly related to their utilization during the process of blood coagulation
2. "Serum accelerator" (accelerin, serum Ac-globulin)
3. "Stable component" (convertin, SPCA: a more active form than in plasma ?)
4. Thrombin and metathrombin

TABLE II

CHARACTERIZATION OF SOME OF THE PLATELET FACTORS[4,98,99]

Platelet factor 1:*
(1) accelerates the conversion of prothrombin to thrombin
(2) water-soluble; precipitated from solution by 50% saturation with $(NH_4)_2SO_4$
(3) sediments following centrifugation at 32,000 r.p.m. for 30 min.
(4) heat labile (53°C.)
(5) non-absorbed on $Ca_3(PO_4)_2$ gel or $BaSO_4$

Platelet factor 2:
(1) accelerates the
$$\text{fibrinogen} \xrightarrow{\text{thrombin}} \text{fibrin reaction}$$
(2) water-soluble; does not precipitate from solution following centrifugation at 32,000 r.p.m. for 30 min.
(3) heat stable
(4) absorbed on $Ca_3(PO_4)_2$ gel and $BaSO_4$; can be eluted from them with sodium citrate

Platelet factor 3:†
(1) opposes the activity of heparin in the blood coagulation process
(2) water-insoluble, suspendable in saline solution
(3) relatively heat stable
(4) non-absorbed on $Ca_3(PO_4)_2$ gel or $BaSO_4$

Platelet thromboplastic factor:†
(1) interreacts with one or more plasma components to form active thromboplastin
(2) found mostly in platelets but also in other formed elements of the blood
(3) water-insoluble, partly soluble in citrate-phosphate buffer solution
(4) heat stable (relatively, at 56°C.)
(5) precipitates following centrifugation at 32,000 r.p.m. for 30 min.
(6) high phospholipid content; similar in chemical structure to placental thromboplastin

* Many of the properties of this factor are shared by the "serum accelerator." The relationship of the two agents is a very close one.

† Platelet factor 3 and platelet thromboplastic factor are very similar in properties and are probably identical agents.

defects are corrected by the addition of normal platelets in *in vitro* tests or, *in vivo*, by the administration of normal viable platelets.[7]

Plasma supplies a number of fairly well characterized factors. (Table I.) *Plasma thromboplastic factor* (thromboplastinogen, antihemophilia. This globulin is found in Cohn's plasma fraction I; it is precipitated quantitatively from diluted plasma by saturation with CO_2 and from whole plasma by 33 per cent saturation with $(NH_4)_2SO_4$. It disappears almost completely during the process of blood coagulation. Platelets, a foreign surface and possibly calcium are required for its utilization. It is very labile on storage, since at least 50 per cent of the activity of the protein disappears in twelve hours at 37°C., and in five weeks at 5°C. from citrated plasma. It is stable for at least six months in frozen or lyophilized plasma. For this reason hemophiliacs in whom control of bleeding is desired should be given recently frozen or lyophilized plasma or, even more effectively, fresh plasma collected within three hours. Plasma thromboplastic factor is stable at 56°C.; it is not precipitated at 32,000 r.p.m. /30 minutes; it is not retained by Seitz filters and is not absorbed on $Ca_3(PO_4)_2$ gel or $BaSO_4$. Interestingly enough, this protein probably represents the globulin factor (coagulase-globulin) which, reacting with staphylo-coagulase, produces coagulase-thrombin, an agent capable of coagulating plasma or purified fibrinogen.[8]

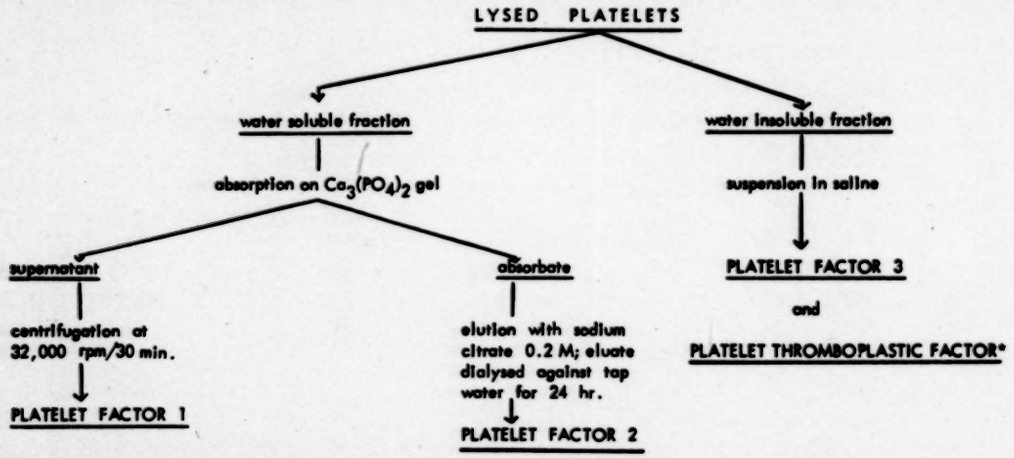

FIG. 2. Crude separation of the platelet factors taking part in the process of blood coagulation.

* No practical method of separation of the two water-insoluble factors is available at present.

philic globulin) is a protein which is apparently required, in addition to the platelet thromboplastic factor and possibly another plasma component, for the activation of thromboplastin. Deficiency of this factor is characteristic of hemo-

TABLE III

THROMBOCYTOASTHENIAS: HEMORRHAGIC DIATHESES DUE TO DEFICIENCIES OF ONE OR MORE OF THE PLATELET FACTORS (A GROUP OF RECENTLY STUDIED CASES) *

Name	Age and Sex	Platelets (x 10^3) (per cu. mm.)	Bleeding Time (Ivy) (min.)	Prothrombin Activity		Clot Retraction (%)
				Plasma (%)	Serum (%)	
E. K.	16, M	567.0	*35*	95	*90*	31
R. D.	6, F	436.8	3	90	17	*2*
G. J.	47, F	549.1	6½	85	*92*	34
R. M.	4, F	501.0	*22*	80	15	39
E. K.	29, F	497.3	4	*30*†	6	32

* Definitely abnormal findings are in italics.

† Non-corrected by administration of vitamin K and vitamin K_1.

The hemostatic defect of case E. K. could be considered due to deficiency of "platelet thromboplastic factor" and of a hypothetical factor controlling the bleeding time ("vascular factor"); that of case R. D. to single deficiency of "retractoenzyme," hypothetical factor responsible for clot retraction; that of case G. J. to a single deficiency of "platelet thromboplastic factor"; that of case R. M. to deficiency of "vascular factor"; that of case E. K. to deficiency of platelet accelerators 1 and 2.

Plasma thromboplastic component (PTC) is a recently postulated factor which remains to be more carefully investigated. Deficiency of this factor is typical of a hemophilia-like condition in which, as in true hemophilia, the utilization of prothrombin during clotting is greatly impaired. The coagulation defect of PTC deficiency is promptly corrected by the addition of hemophilic plasma, but not of normal platelets, to the patient's plasma.[9,10] Prothrombin consumption, as determined with the available technics, is significantly reduced when the activation of thromboplastin is impaired, as in

hemophilia (deficiency of plasma thromboplastic factor) or in thrombocytopenia (deficiency of platelet thromboplastic factor). It should be concluded then, that PTC is required, in addition to the other two factors, for the activation of thromboplastin in physiologic conditions. This factor is found in the serum euglobulin and pseudoglobulin fractions, is precipitated at 40 to 50 per cent saturation with $(NH_4)_2SO_4$ (plasma thromboplastic component or antihemophilic globulin is precipitated at 33 per cent saturation), and is active over a wide range of pH (from 4 to 11.2). It is heat- and storage-stable, is removed by Seitz filters and absorbed on $Ca_3(PO_4)_2$ gel and $BaSO_4$ from which it can be eluted with sodium citrate. This last property is utilized in the partial purification of PTC. Platelet-poor oxalated plasma heated at 56°C. for five minutes (to coagulate fibrinogen) is cooled in ice. Fibrinogen is removed by centrifugation and the plasma absorbed with 50 mg. of $BaSO_4$ per ml. After centrifugation the precipitate is washed with 0.02 M acetate buffer and is again separated by centrifugation at 3,000 per 30 minutes. Finally, PTC is eluted with 5 per cent sodium citrate in 0.9 NaCl, the solution is dialyzed against 0.9 per cent NaCl solution at 4°C. for twenty-four hours and lyophilized.[10] It is obvious that the new factor shares many properties of the "stable component" and it is known that the latter partly corrects the impaired prothrombin consumption of hemophilic blood.[11] More detailed study will be required before the existence of this agent is fully established.

Prothrombin, a sulfur containing glycoprotein, is the key substance in the process of thrombin formation. It is recovered in Cohn's fraction III-2 and its electrophoretic mobility is that of α_1 globulin. It is water soluble and relatively heat stable since inactivation begins at 40°C. and is complete at 60°C. in purified preparations. In plasma, prothrombin will resist temperatures of 56°C. for five minutes. Its isoelectric point is at pH 4.2. The globulin contains approximately 14 per cent N, 4.6 per cent tyrosine, 3.3 per cent tryptophane, 0.96 per cent sulfur, 4.3 per cent sugar, etc. Prothrombin is very stable in plasma frozen or lyophilized shortly after collection; at 5°C., in citrated plasma, its activity remains constant for at least twenty-one days. It is retained by Seitz filters and absorbed on $Ca_3(PO_4)_2$ gel and $BaSO_4$ from oxalated, but not from citrated plasma. From the gel it can be eluted with sodium citrate solution.

Prothrombinogen, an inactive precursor of prothrombin,[12,13] tends to yield active prothrombin during storage. Foreign surfaces (but not platelets or calcium) are necessary for activation. Prothrombinogen is depressed during dicumarol® administration, is normal in hemophilia. It is deficient in one type of hemorrhagic diathesis characterized by prolonged one-stage prothrombin time but in which prothrombin itself and labile component are normal in activity. Prothrombinogen can be absorbed from oxalated plasma on $Ca_3(PO_4)_2$ gel or $BaSO_4$ and subsequently eluted with sodium citrate. From the description of its properties, prothrombinogen is very closely related to the "stable component." Its mechanism of activation, however, would appear to distinguish this agent from all others.

Calcium probably takes part in all phases of the coagulation process although its major role is in the conversion of prothrombin to thrombin. This step may require preliminary binding of calcium to the labile component.[14] When blood is collected using sodium citrate as anticoagulant, as well as by ion-exchange resins, thereby incompletely removing calcium, the destruction of the labile component on storage is greatly decreased.[15]

"*Labile component*" (proaccelerin, labile factor, plasma Ac-globulin) is an agent which either accelerates or is indispensable to the conversion of prothrombin to thrombin. This agent is a water-soluble globulin, promptly inactivated by heat (58°C.), trypsin and fibrinolysin. Its activity is unmodified over a wide range of pH (4 to 10.5). Especially in the absence of calcium, this agent is extremely labile on storage (hence its name). In citrated plasma, however, it is stable for at least one week at 5°C.; and at least 50 per cent and 30 per cent activity is still present after two and three weeks of storage, respectively. This factor is only minimally absorbable on $Ca_3(PO_4)_2$ gel or $BaSO_4$, is filtered through Seitz and 40 to 50 per cent asbestos filters. It is precipitated from diluted plasma by 10 per cent ether in the cold, by acid at pH 5.4 and by 45 per cent saturation with ammonium sulfate. The concentration of the labile component is not affected appreciably by dicumarol.[16] (Table IV.)

In the presence of small amounts of thrombin, or during the process of blood coagulation, "*serum accelerator*" (accelerin, serum Ac-globulin)

develops from the labile component. Like the latter, serum accelerator reduces the clotting and prothrombin time of aged plasma, and greatly accelerates the conversion of prothrombin to thrombin. It is extremely labile in storage, disappearing as soon as thirty minutes after the clotting of blood. It is only minimally absorbed on $Ca_3(PO_4)_2$ gel.

TABLE IV

CHARACTERISTIC DIFFERENTIAL PROPERTIES OF "STABLE" AND "LABILE" COMPONENT*

	Stable Component	Labile Component
Where found	Plasma and serum (possibly in more active form in the serum)	In plasma; after activation by thrombin, "serum accelerator," a derivative of the labile component, is found in the serum
Coagulability of aged plasma on addition of each component	Unaffected	Restored to normal
Heat stability	Resistant at 56°C. for 30 minutes	Inactivated immediately at 58°C.
Stability on storage	Very stable during storage of plasma and serum	Very labile on storage, especially in the absence of calcium
Absorption on $Ca_3(PO_4)_2$ gel, $BaSO_4$ and Seitz filters	Absorbed specifically (also on 30% asbestos filters); can be, like prothrombin, specifically eluted from these gels and filters with sodium citrate	Minimally or not absorbed
Fate during coagulation of blood	Probably not utilized or only little utilized	Activated to "serum accelerator" by thrombin; the concentration of this component remaining in the serum and non-converted to serum accelerator is related to the extent of the conversion of prothrombin to thrombin
Effect of dicumarol therapy and vitamin K deficiency on the activity of each agent	Prompt reduction in activity induced by dicumarol therapy and vitamin K deficiency, response to vitamin K in both conditions comparable to that of prothrombin	None or very slight

* The designations of "stable" and "labile' component used throughout this review have not been chosen with the intention of recommending their adoption but because they have been useful in the understanding of the subject and they underline one of the most significant differential properties of the two agents.

"*Stable component*" (proconvertin, plasma precursor → serum prothrombin conversion accelerator: SPCA, factor VII) is also postulated to accelerate the rate of conversion of prothrombin to thrombin. This agent, however, does not shorten the clotting or prothrombin time of aged plasma. No definite evidence is available that this agent is utilized to any appreciable extent in the process of blood coagulation. Consequently, it is found in approximately identical concentration in serum and plasma.* Its activity is normal in hemophilia but it is promptly affected by dicumarol therapy. This agent is relatively heat stable (56°C. for thirty minutes), stable on storage of plasma and serum (it represents the only coagulation factor left in normal human serum stored for ten days at 5°C.), and it is not dialyzable. Its optimal activity is over a more limited range of pH than the labile component (4 to 8). It can be absorbed, like prothrombin, on $Ca_3(PO_4)_2$ gel or $BaSO_4$ and eluted from these with sodium citrate. It can be precipitated from the eluate by 90 per cent saturation with $(NH_4)_2SO_4$. Stable component of cow (but not human) plasma is retained on 30 per cent asbestos filters. (Fig. 3.) It is obvious that the stable component shares many properties of prothrombin, and the possibility that stable component is a prothrombin derivative cannot be excluded. There are, however, several findings previously summarized which indicate the individuality of the two agents, such as the different behavior in stored serum. The most significant point in

* Some investigators,[17,18] however, believe that the stable component is converted to a more active agent during the process of blood coagulation (proconvertin → convertin; plasma precursor → SPCA).

favor of the individuality of prothrombin, stable component and labile component is probably the discovery of patients in whom the bleeding tendency is due to the deficiency of one or the other of these factors. Thus deficiency of either prothrombin or labile component, congenital or acquired, has been recognized for some time. At present, cases are being studied[18,19,20] of patients with bleeding tendency characterized by delayed prothrombin time best corrected by addition of purified stable component *in vitro* and by administration of serum *in vivo*. As previously stated, serum is lacking or very poor in prothrombin and labile component while rich in stable component. Cases of this type probably represent primary stable component deficiency. That serum accelerator and stable component of serum are not identical is indicated by two facts: (1) the serum accelerator is very labile on storage whereas the stable component is not; and (2) the extinction coefficient of the two substances in the ultraviolet range is definitely different. Since much of the confusion existing at present has been due to failure to realize the nature and activity of labile and stable component, Table IV gives a short outline of the fundamental differences between these two components. Figure 3 presents a scheme of simple procedures for the crude separation of prothrombin, stable and labile component. These purified preparations can be usefully employed as reagents in the determination of prothrombin, labile and stable component. (Table V.)

Fibrinogen is a globulin with a molecular weight of 400,000, an approximate isoelectric point of 5.3, a sedimentation constant (S_{20}, w) of 9, an intrinsic viscosity of 25 (Ho.10^2) and approximate dimensions of 700 (length) and 38 (diameter) Å. It is therefore a very asymmetrical protein and apparently owes many of its properties to this asymmetry. It coagulates irreversibly at 56°C.; it is reversibly precipitated at 50 per cent saturation with NaCl, 25 per cent saturation with $(NH_4)_2SO_4$, by 8 per cent ethanol in the cold and by weak acids. Fibrinogen is present in fraction I-2 of Cohn; lyophilized under vacuum, this fraction can be kept indefinitely. Another technic of preparation consists in freezing oxalated plasma at −30°C. and then slowly warming the preparation to 5°C. Fibrinogen is precipitated, washed repeatedly with cold distilled water, finally dissolved in saline solution at 37°C. and lyophilized.[21] Both methods yield fibrinogen relatively free of fibrinolysin and other coagulation factors. Fraction I-2 has been used successfully in topical form, and parenterally in the treatment of congenital afibrinogenemia and of the severe hypofibrinogenemia which follows premature separation of placenta.

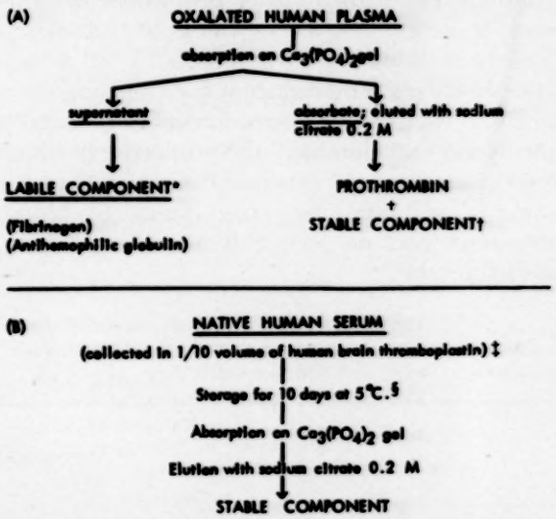

FIG. 3. Crude separation of the plasma factors taking part in the conversion of prothrombin to thrombin.

* The labile component can be specifically precipitated by acidifying the diluted plasma to pH 5.4.

† In cow plasma prothrombin and stable component can be easily separated (although with large loss of both factors) by filtering the plasma through 30 per cent asbestos filter.[17] The stable component is retained on the filter, prothrombin passes through. The stable component can then be eluted with sodium citrate from the filter pad.

‡ To produce complete utilization of prothrombin, thus eliminating this agent from the serum.

§ To cause destruction or inactivation of the labile component non-utilized during the process of blood coagulation and of the "serum accelerator" developed during the clotting of blood.

In addition to factors favoring the process of blood coagulation, plasma contains agents which oppose the clotting of blood (antithromboplastin, antithrombin, albumin X) and agents which may lyse, under certain conditions, the formed clot (profibrinolysin, antifibrinolysin, antifibrinolysokinase). All these agents will be discussed subsequently. (Table VI.)

Serum contains, with the exception of fibrinogen, all factors found in plasma in concentrations directly related to the extent of their utilization during the process of blood coagulation. Thus very little prothrombin or labile component is left in serum after completion of clotting under normal conditions. In thrombo-

cytopenia or hemophilia, however, in which the activation of thromboplastin and therefore the conversion of prothrombin to thrombin is impaired, high prothrombin and labile component activity is found in the serum, which also exhibits little accelerator activity,[22] shortly after clotting. The utilization of prothrombin, however, is merely delayed by the slow and incomplete activation of thromboplastin; it is not completely prevented since it goes to completion in six to twenty-four hours. Serum also contains the "serum accelerator," the properties of which have already been described and, at least for some time after the coagulation of blood, thrombin and its reversibly inactivated form, metathrombin.

THE NORMAL MECHANISM OF BLOOD COAGULATION

Morawitz's original theory visualized the process of coagulation of blood as occurring in two successive enzymatic reactions:

1. Prothrombin $\xrightarrow{\text{Thromboplastin}}$ Thrombin
2. Fibrinogen $\xrightarrow[\text{Thrombin}]{Ca^{++}}$ Fibrin

This theory represented a very useful working hypothesis for many years until more recent developments rendered it obsolete. As a result of the work of many investigators it is recognized today that: (1) activation of thromboplastin is a separate, preliminary phase in the

TABLE V

PRINCIPLES OF THE TECHNICS FOR THE DETERMINATION OF PROTHROMBIN, STABLE AND LABILE COMPONENT*

Reagents added	Factors Kept Constant	Factor Determined
Plasma under study (diluted 10%) + a. Fresh human oxalated plasma, treated with $Ca_3(PO_4)_2$ gel to remove prothrombin and stable component	Labile component, Fibrinogen	Prothrombin + Stable component
+ b. Human brain suspension†	Thromboplastin	
+ c. $CaCl_2$ 0.02 M	Calcium	
+ a. Stored human serum	Stable component	
+ b. Fresh human oxalated plasma, treated with $Ca_3(PO_4)_2$ gel, to remove prothrombin and stable component	Labile component, Fibrinogen	Prothrombin
+ c. Human brain suspension	Thromboplastin	
+ d. $CaCl_2$ 0.02 M	Calcium	
+ a. Fresh oxalated ox plasma, passed through 30% asbestos filter, to remove stable component	Prothrombin, Labile component, Fibrinogen	Stable component
+ b. Human brain suspension	Thromboplastin	
+ c. $CaCl_2$ 0.02 M	Calcium	
+ a. Stored human oxalated plasma	Fibrinogen, Prothrombin, Stable component	Labile component
+ b. Human brain suspension	Thromboplastin	
+ c. $CaCl_2$ 0.02 M	Calcium	

* The fundamental principle of all these technics is that of maintaining constant in the reacting mixture all factors but the one which is being determined. All reagents, including the plasma under study, are added in the volume of 0.1 ml.

† Saline suspension of fresh or acetone-dehydrated human brain.

An alternative, very satisfactory technic for the combined determination of prothrombin and stable component is as follows: prothrombin and stable component are absorbed from the plasma studied with $Ca_3(PO_4)_2$ gel; they are subsequently eluted with 1/10 volume of sodium citrate; 0.09 ml. of fresh human oxalated, $Ca_3(PO_4)_2$ treated plasma are added to 0.01 ml. of the eluate to reconstitute the reacting mixture by adding labile component and fibrinogen, and the prothrombin time of the mixture is determined.[101,102]

It may be added here that, since prothrombin and stable component are both decreased during dicumarol therapy and both factors influence the results of the one-stage method of Quick, this test appears very adequate in the control of anticoagulant therapy with antiprothrombic drugs, since it expresses the over-all coagulability of plasma.

formation of thrombin; (2) other factors, besides thromboplastin and calcium, take part in the conversion of prothrombin to thrombin; (3) serum contains agents accelerating the conversion of prothrombin to thrombin; (4) the formation of thrombin during the coagulation of blood proceeds as an autocatalytic reaction. Physiologic anticoagulants play an apparently important role in regulating the speed and completeness of the autocatalytic reaction. Many of these newer concepts were, it should be noted, proposed by early investigators: thus, Collingwood and MacMahon[23] postulated the preliminary phase of activation of thromboplastin in 1912; as early as 1904 Bordet[25] recognized the presence in serum of agents accelerating the conversion of prothrombin to thrombin; in 1908 Nolf[24] insisted that at least one agent other than thromboplastin and calcium entered into the formation of thrombin from prothrombin. These ideas went unnoticed in their own time. Today, however, they are fully accepted and, as a result of these and other findings, blood coagulation is visualized as a three-step process: (1) activation of thromboplastin; (2) conversion of prothrombin to thrombin; (3) formation of fibrin. The nature of these reactions, whether enzymatic or stoichiometric, is still hotly disputed.

Active thromboplastin is found in water and alcohol extracts of many tissues, particularly lung and brain. The water soluble substance is a relatively heat-stable lipoprotein. Its lipid fraction is a mixture of phospholipids, cholesterol, etc., and cephalin probably represents the active principle. Alcohol extracts of tissues also exhibit thromboplastic activity, due to a heat stable lipid (probably cephalin). A description of the characteristic properties and chemical nature of thromboplastins is omitted for the sake of brevity, the interested reader being referred to original publications by Howell,[26] Quick[27] and Chargaff.[28]

An entirely different situation exists in the circulating blood. Since plasma collected with special precautions to prevent platelet breakdown and made platelet-free by centrifugation at high speed will not clot for an indefinite time,[29] probably no free thromboplastic material is present in plasma. Increasing evidence supports the view that thromboplastin is found in plasma as an inert precursor and that its activation (which occurs most commonly at the time of vascular injury) requires the inter-

TABLE VI

SYNONYMS OF VARIOUS FACTORS ACTIVE IN THE COAGULATION OF BLOOD

1. Factors taking part in the activation of thromboplastin:
   Platelet thromboplastic factor:
   - thromboplastinogenase[31]
   - cellular thromboplastic component (TCC)[30]

   Plasma thromboplastic factor:
   - prothrombokinase[78]
   - plasmakinin[79]
   - antihemophilic globulin[80]
   - thromboplastinogen[31]
   - thrombocytolysin[32]
   - thrombokatalysin[81]
   - thromboplastic plasma component (TPC*)[30]
2. Thromboplastin (tissues):
   - thrombokinase
   - cytozime[24]
   - thromboplastic protein[28]
   - thrombokinin[81]
3. Factors involved in the conversion of prothrombin to thrombin other than calcium and thromboplastin:

   "Labile component":
   - thrombogéne[24]
   - component A of prothrombin[82]
   - factor V → factor VI[83]
   - accelerator factor[84]
   - labile factor[85]
   - co-factor of thromboplastin[86]
   - plasma Ac-globulin → serum Ac-globulin[87]
   - proprothrombinase → prothrombinase[88]
   - prothrombinogenase → thrombinogenase[88]
   - ? prothrombinokinase → thrombokinase (†)[89]
   - plasma prothrombin conversion factor (PPCF) → serum accelerator[90]
   - proaccelerin → accelerin[91]

   "Stable component":
   - co-factor V[88]
   - ? component B of prothrombin[85]
   - prothrombin accelerator[92]
   - prothrombin conversion factor[93]
   - prothrombin converting factor[94]
   - co-thromboplastin[95]
   - plasma precursor → serum prothrombin conversion accelerator (SPCA)[96]
   - proconvertin → convertin[91]
   - factor VII[35]
   - ? prothrombinogen (inactive prothrombin)[13]
   - kappa factor (in chicken)[97]

* Not to be confused with plasma thromboplastic component (PTC) (see text).

† Signifying an agent capable of influencing the conversion of prothrombin to thrombin.

Many of the factors of group 3 are very likely mixtures of "labile component" and "stable component" or, even more probably, of prothrombin and "stable component." Some of these factors are arranged in couples, joined by an arrow. Those at the right of the arrow are considered less active precursors found in plasma; those at the left, the active (or more active) form found in the serum. For this reason some investigators prefer to think of "labile" and "stable component" in terms of a system and not as isolated factors.

reaction of a plasma factor (plasma thromboplastic factor, thromboplastinogen, anti-hemophilic globulin) and a platelet factor (platelet thromboplastic factor). The properties and nature of the plasma and platelet thromboplastic factors have already been discussed; the latter has properties very similar to those of placental thromboplastin.[30] The reaction of the two agents has been variously interpreted as an enzymatic action of the platelet factor on the plasma factor[31] or, *vice versa*, as resulting in lysis of platelets induced by the plasma factor ("thrombocytolysin")[32] which apparently liberates platelet thromboplastic lipoprotein, etc. Careful work by Shinowara[30] seems to indicate that the blood cell (platelet) lipoprotein and the non-clottable globulin of fraction I (anti-hemophilic globulin) together, but not separately, constitute a factor identical with tissue thromboplastin in respect to prothrombin activation. The interreaction is probably regulated by the law of mass action (stoichiometric).

These investigations all emphasize the primary role of the platelets in the coagulation of blood. It has been stated that contact of plasma thromboplastic factor (anti-hemophilic globulin) with a foreign surface is a prerequisite to reaction with the platelet lipoprotein.[33] More recently, the problem has been further complicated by the discovery of a plasma factor (PTC), deficiency of which is responsible for abnormally low utilization of prothrombin during clotting. Theoretically, at least, this agent should be involved in the activation of thromboplastin.

It is now generally recognized that, besides thromboplastin and calcium, at least one additional factor (labile component) takes part in the second phase of the coagulation process, the conversion of prothrombin to thrombin. The role of the stable component is also gaining increasing acceptance.

The kinetics of this phase are still open to question. Experimental results can be quoted to prove the stoichiometric or enzymatic nature of the conversion of prothrombin to thrombin, at will. Thus (1) thrombin does not contain thromboplastic material or ionic calcium (but may contain bound calcium); (2) the molecular weight of thrombin is smaller than that of prothrombin; (3) thrombin evolves slowly but spontaneously in a solution of purified prothrombin in 25 per cent sodium citrate;[34] (4) the stable component is probably not utilized during the process of blood coagulation.[35] If one accepts these results, it must be concluded that the prothrombin molecule contains all the materials necessary for the formation of thrombin and that, in effect, calcium, thromboplastin, stable and labile component are merely "accessory factors" influencing only the rate of prothrombin conversion. On the other hand: (1) the concentrations of available thromboplastin[36] and of calcium are the limiting factors in the amount of prothrombin which can be converted to thrombin; (2) labile component is utilized quantitatively in the formation of thrombin,[37,38] serum accelerator evolving at the same time; (3) no thrombin can apparently evolve in a mixture of prothrombin, thromboplastin and calcium in the absence of labile component.[39] These findings would suggest that prothrombin, calcium, thromboplastin and, at least, labile component interreact according to definite proportions, thus indicating that the reaction is stoichiometric in nature. All these experiments are not above criticism. Thus the "purity" of many of the isolated coagulation factors used in these experiments is problematic. On the other hand, the decrease in concentration or activity of any coagulation factor during the formation of thrombin is not definite evidence of a stoichiometric reaction, especially when it is known that, while some of these factors decrease, more active derivatives develop as a result of thrombin formation. No definite conclusion as to the nature of the phase of blood coagulation leading to the formation of thrombin can yet be reached. It should be pointed out, however, that while experiments *in vitro* may indicate that thromboplastin, labile and stable component only regulate the rate of thrombin formation, even interchangeably, and may be fundamentally unnecessary for the conversion of prothrombin to thrombin, marked deficiency of any one of these factors *in vivo* is usually accompanied by severe bleeding manifestations, an indication that the hemostatic mechanism has become grossly inadequate. From the clinician's point of view, effective protection against hemorrhage requires the presence in concentrations above the critical level of *all* factors known to play a role in the coagulation of blood.

There is no doubt as to the enzymatic nature of the fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin reaction. Thrombin, which evolves during the coagulation of blood, is probably an albumin, contain-

ing sulfur and approximately 5 per cent carbohydrate. It is precipitated at pH 5.1 to 3.4, is water soluble, and has a molecular weight lower than that of prothrombin. Thrombin is heat labile, its inactivation beginning at 40°c. and is completed at 60°c. It is possible, although not definitely proven, that thrombin is a product of the degradation of prothrombin. Thrombin, although capable of destroying prothrombin at low concentrations, is not a proteolytic enzyme and is distinct from fibrinolysin. Although not utilized at present for therapeutic uses parenterally, its local use, with oxycellulose, fibrin foam, etc., has greatly improved the technics of control of local bleeding.

Gelification of fibrinogen to form fibrin in the presence of thrombin does not involve any profound intramolecular change. Fibrinogen and fibrin are chemically identical, and have identical antigenic properties and x-ray diffraction. They yield identical degradation products on enzymatic digestion. The molecules of fibrinogen are rearranged to form fibrin without losing their individuality. After a preliminary end-to-end rearrangement[40] the long molecules of fibrinogen undergo a process of tri-dimensional polymerization.[41] Most investigators in this field think that the binding of the individual fibrinogen molecules takes place through the sulfhydril group (S-H). When molecules of fibrinogen come together these groups are oxidized by thrombin to S-S groups. Different theories have been presented by Laki[42] and Mommaerts.[43] According to Lyons,[44] the fibrinogen $\rightarrow$ fibrin reaction occurs in two steps: first, the S-H groups of fibrinogen are freed; secondly, the S-H groups are oxidized, probably by the activity of the naphthoquinone groups present in the thrombin molecule. At the end of the first step, an easily identifiable fibrinogen derivative would be expected to be present, namely, fibrinogen B. Cummine and Lyons[45] have stated that fibrinogen B can be found in the circulating blood of patients with thromboembolism or thrombotic tendency and, since fibrinogen B can be precipitated by the addition of β-naphthol, they have recommended the qualitative detection of fibrinogen B as a test of thrombotic tendency. Unfortunately, little correlation has been found between this test and actual thromboembolism.

The enzymatic nature of the fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin reaction is further indicated by the fact that thrombin can clot approximately 10^5 times its weight in fibrinogen. Calcium is not necessary for this reaction but its presence greatly enhances the activity of thrombin. It is possible that thrombin might unite temporarily with fibrinogen while this is converted to fibrin. This fibrinogen-thrombin reversible combination may represent a less soluble, less stable and already partially denatured fibrinogen derivative (different from fibrinogen B), defined by Apitz[46] as *profibrin*.

At this point it would be helpful to indicate how various investigators in the field* visualize the details of the process of blood coagulation, using diagrams prepared for the Handbook of Biological Data by Dr. E. C. Albritton. The schemes are in cyclical form, a device which conveniently emphasizes the autocatalytic nature of the process of blood coagulation. Physiologic anticoagulants are also included. The fibrinolytic system is excluded in view of its uncertain role in the physiologic coagulation of blood.

According to Owren, coagulation begins when thromboplastin is made available through tissue injury or through the release of prothromboplastin when platelets disintegrate by contact with a foreign surface. Prothromboplastin is then activated to thromboplastin, also by contact, but in the presence of calcium and antihemophilic globulin. Thromboplastin and calcium convert proconvertin to convertin ("stable component"). Convertin, together with calcium, brings about a minimal conversion of prothrombin to thrombin. This thrombin, while inadequate for gelification of fibrinogen, can convert proaccelerin ("labile component") to accelerin ("serum accelerator"). When accelerin is activated, the interreaction of prothrombin, calcium, thromboplastin and convertin to form thrombin is greatly accelerated and thrombin is now formed in sufficient quantity to convert fibrinogen to fibrin. The fibrin clot, acting as a foreign surface, causes disintegration of platelets and release of prothromboplastin, thus establishing an autocatalytic cycle. (Fig. 4.)

Quick's theory is somewhat simpler. Thromboplastin is released by tissues or is formed by the interreaction of a platelet factor (thromboplastinogenase) and a plasma factor (thromboplastinogen). In a second phase, thromboplastin, calcium, labile factor ("labile compo-

* Presented in alphabetic order.

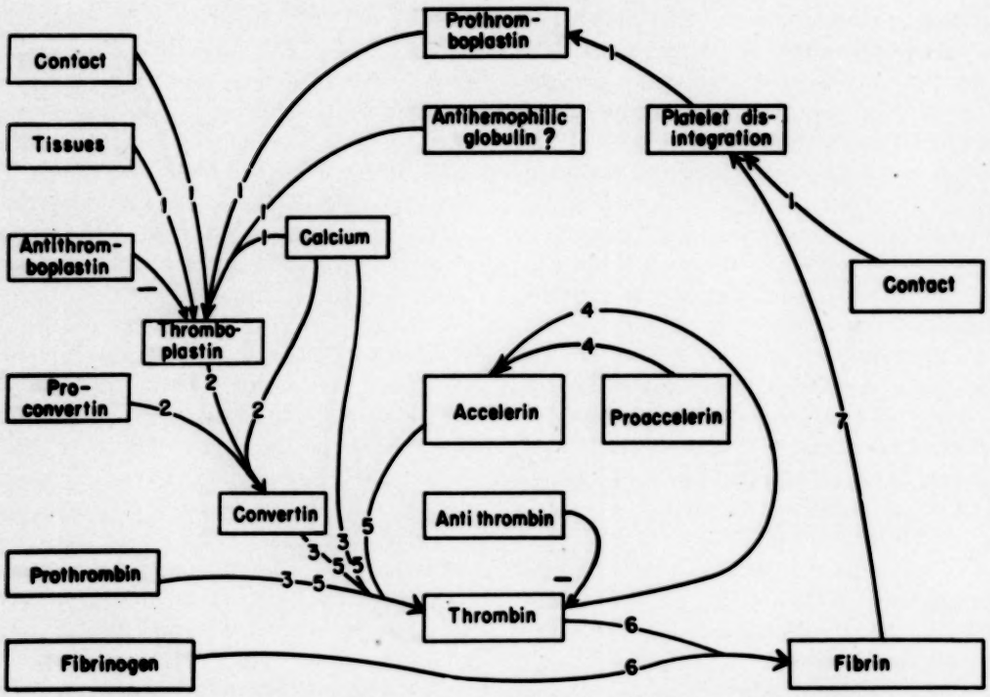

FIG. 4. Blood coagulation: theory of P. A. Owren (1952) (explanation in the text).*

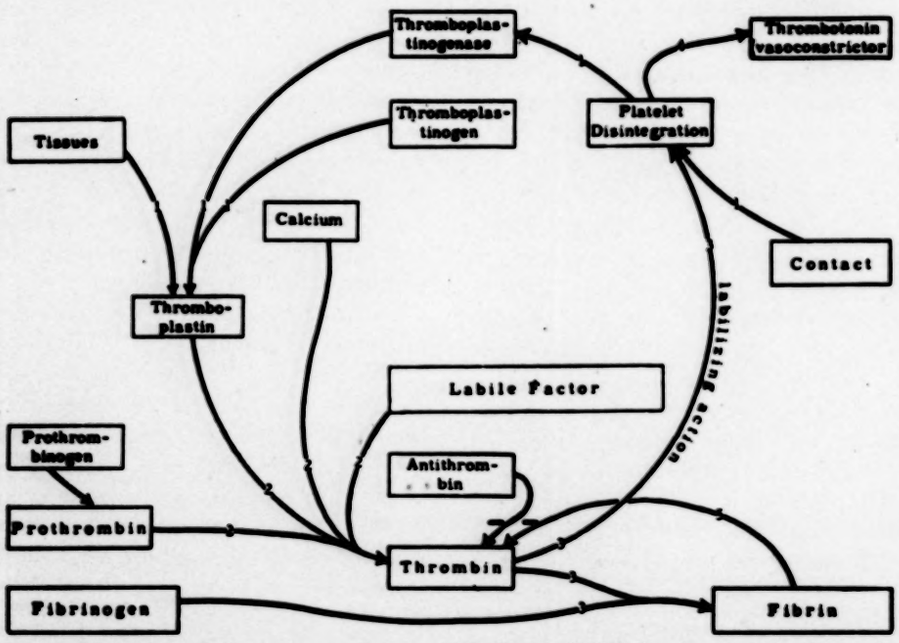

FIG. 5. Blood coagulation: theory of Armand J. Quick (1951) (explanation in the text).

nent") and prothrombin interreact stoichiometrically to form thrombin. Also, an inactive prothrombin precursor (prothrombinogen) is activated to prothrombin by the action of rough surfaces. The thrombin formed not only converts fibrinogen to fibrin but also "labilizes" platelets, affording the release of more thromboplastinogenase and, consequently, the formation of more thrombin. The fibrin clot exercises a very important function since, by adsorbing thrombin, it checks the ever accelerating forma-

* Figures 4 to 8 are published through the courtesy of Dr. Errett C. Albritton and the Handbook of Biological Data.

tion of this enzyme which occurs during the coagulation of blood. (Fig. 5.)

Seegers believes that platelet disintegration due to contact causes the release of thromboplastin agent (which reacts with antihemophilic globulin to produce thromboplastin) and two platelet accelerator principles. Thromboplastin is also yielded directly by injured tissues. Thromboplastin and calcium, together with platelet accelerator 1, cause a minimum conversion of prothrombin to thrombin and this initial conversion starts the accelerator phase, namely, the conversion of plasma Ac-globulin ("labile component") to serum Ac-globulin ("serum accelerator"). Thromboplastin, calcium, platelet accelerator and serum Ac-globulin cause accelerated conversion of prothrombin to thrombin. This enzyme together with platelet accelerator 2 converts fibrinogen to fibrin. Again fibrin checks the accelerated formation of thrombin by adsorbing the enzyme on its surface. (Fig. 6.)

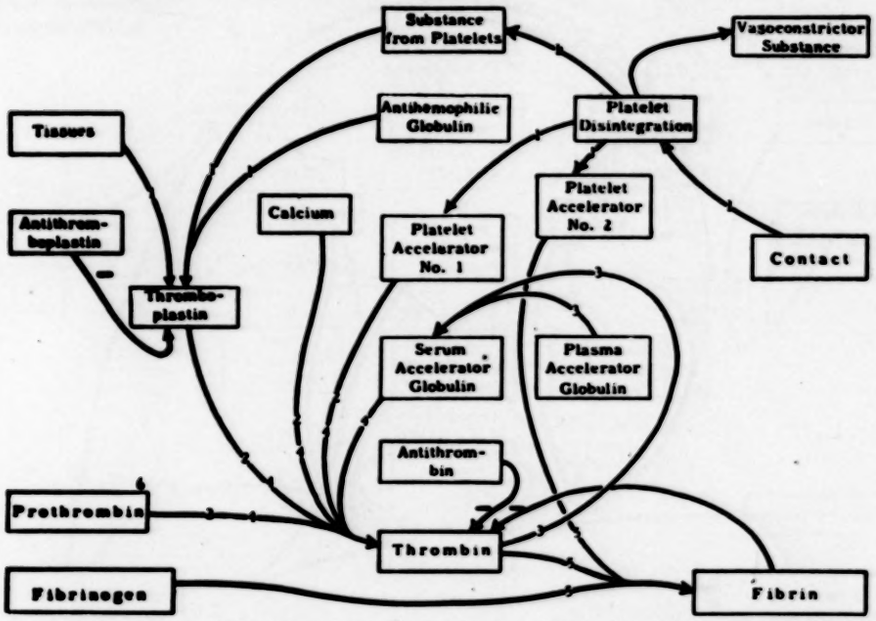

FIG. 6. Blood coagulation: theory of W. H. Seegers (1951) (explanation in the text).

According to Tocantins, injured tissue releases thromboplastin while disintegrating platelets release thromboplastin and an accelerator substance. Thromboplastin and calcium effect a minimal conversion of prothrombin to thrombin. This thrombin activates plasma Ac-globulin to serum Ac-globulin and the interreaction of this latter agent with thromboplastin, calcium and prothrombin causes greatly accelerated formation of thrombin. Thrombin converts fibrinogen to fibrin with the help of the platelet accelerator substance 2 (platelet factor 2). Fibrin checks the autocatalytic reaction by adsorbing thrombin while, at the same time, it causes further disintegration of platelets with release of thromboplastin factors. (Fig. 7.)

A careful analysis of the four schemes indicates certain fundamental similarities and dissimilarities. Most of the disagreement involves the phase of blood coagulation process in which prothrombin is converted to thrombin, a point already discussed. Quick states that no accelerators* take part in the formation of thrombin and that prothrombin, thromboplastin, calcium and labile factor interreact according to stoichiometric proportions.

Seegers and Tocantins postulate the existence of one accelerator system (plasma Ac-globulin → serum Ac-globulin = labile component → serum accelerator). Owren assumes one accelerator system (proaccelerin → accelerin) as well as one convertor system (proconvertin → convertin = stable component).

Despite the disagreement, however, there are some fundamental conclusions subscribed to by all authors: (1) All agree that agglutination or disintegration of platelets represents the initial

* It has already been noticed that Quick and Stefanini's prothrombinogen is probably similar to the stable component.

step in the coagulation of blood. It initiates the activation of thromboplastin, the first step in the clotting process; it supplies a vasoconstrictor principle which causes a prolonged, generalized state of vasoconstriction, thus reducing blood loss and favoring a firm anchoring of the clot

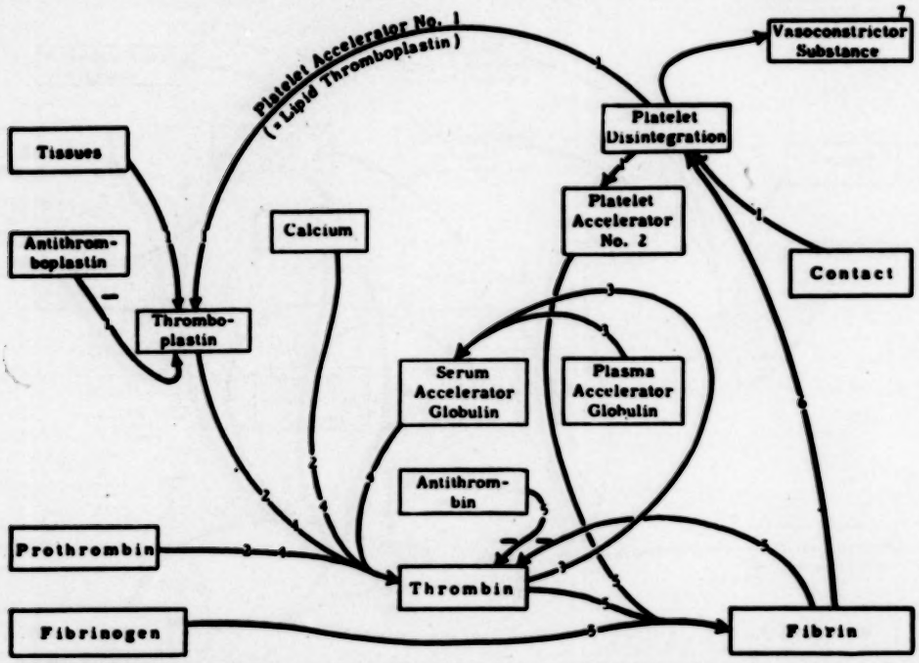

FIG. 7. Blood coagulation: theory of L. M. Tocantins (1951) (explanation in the text).

of fibrin.[47] (2) One or two factors besides thromboplastin and calcium are necessary for the optimal conversion of prothrombin to thrombin. (3) Fibrin, far from being an inert product of blood coagulation, plays an active role in it. On the one hand, it absorbs thrombin on its surface and therefore checks the tumultuous formation of this enzyme; on the other, it probably labilizes platelets in the manner of any rough surface, liberates more thromboplastin activator, and thus contributes to continuation of the autocatalytic reaction. (4) The process of blood coagulation is a delicate, unstable balance between positive and negative forces, which multiple factors and conditions can easily influence positively or negatively. All diagrams mention two physiologic anticoagulants, antithromboplastin and antithrombin. Others may well be present. Thus Owren suggests physiologic inhibitors for the active form of both labile and stable component (antiaccelerin and anticonvertin). It should not be forgotten, however, that at times the inhibitory action of plasma upon various clotting factors may be due to absorption on other proteins, like fibrin and, possibly, other globulins, rather than to the presence of specific anticoagulants. Little is known of *antithromboplastin*, the very existence of which is still doubted by some investigators. *Antithrombin* is present in the albumin fraction of plasma and serum and is inactivated at 67°C. Albumin X or heparin co-factor and natural antithrombin may be one and the same substance or they may represent two different substances in the same plasma and serum fractions. Physiologic antithrombin probably acts by absorbing thrombin on its surface. The combination of thrombin and antithrombin (for which calcium is not necessary) constitutes *metathrombin*. This combination may be split by addition of alkalies or acids, thrombin being recovered intact after neutralization. This constitutes additional proof of the enzymatic nature of thrombin.

Early investigators had concluded[48] that the process of thrombin formation is greatly accelerated after a small amount of the enzyme has been formed. This hypothesis had been based on very simple but significant experiments. Thus if one follows the coagulation of blood in a test tube, no appreciable change in the physical state of the blood takes place for several minutes; then in a short fraction of time the blood turns solid. It appeared evident to

Arthus that there must be a preliminary phase of blood coagulation during which a product was formed which could greatly accelerate its own formation; he thought this could be thrombin. Rightly, therefore, all present investigators emphasize the role of the auto-

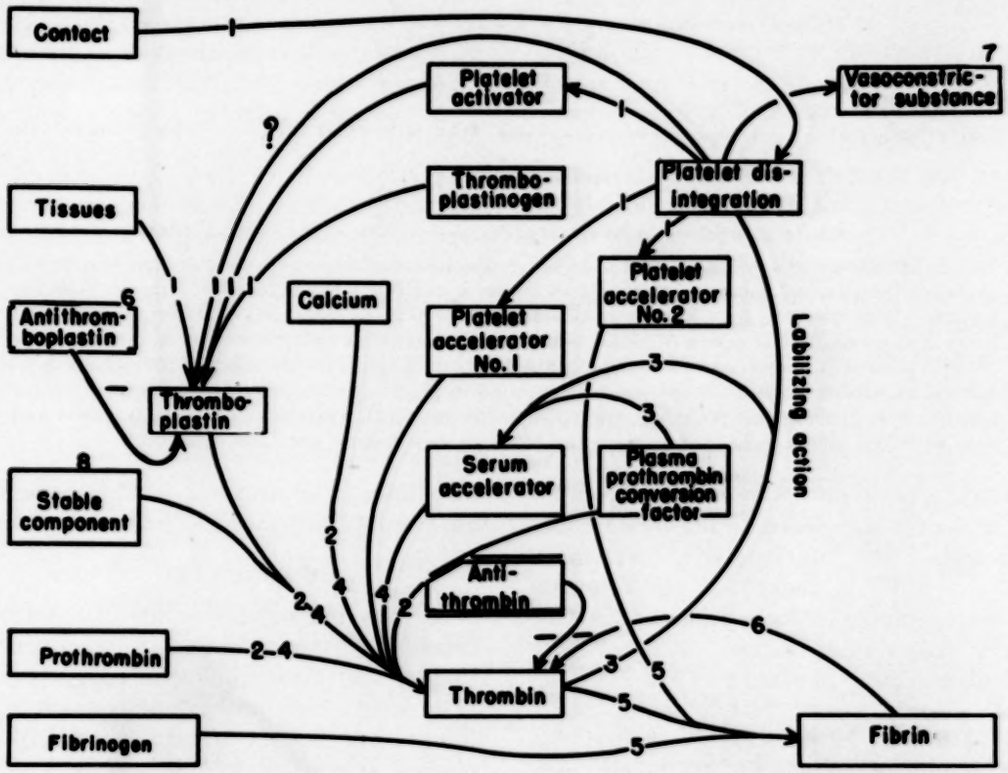

FIG. 8. Blood coagulation: theory of M. Stefanini (1952) (explanation in the text).

catalytic mechanism in blood coagulation. The writer (Fig. 8) divides the process of blood coagulation into a "slow phase" and an "accelerated phase." The latter phase is due to the initiation and continuation of the autocatalytic reaction. The slow phase initiates when platelets disintegrate and ends with the formation of small amounts of thrombin; the accelerated phase initiates with the activation of the accelerator system and ends with the conversion of fibrinogen to fibrin. The first fundamental step in the entire process, the agglutination of platelets, follows any lesion involving the vascular endothelium. Platelet disintegration determines release of an agent (platelet activator = platelet thromboplastic factor) which, reacting with a plasma component (thromboplastinogen = plasma thromboplastic factor), determines formation of thromboplastin. It is possible that platelets may release thromboplastin directly but, in any case, in minimal amounts. Prothrombin, thromboplastin, calcium, plasma prothrombin conversion factor (labile component) and stable component react to form a small amount of thrombin. Once thrombin has been formed, the plasma prothrombin conversion factor is activated to "serum accelerator." Prothrombin, calcium, "stable component," thromboplastin, "serum accelerator" interreact in the course of the accelerated phase of the coagulation process, which now proceeds at increasing speed. Once enough thrombin has been formed, it promptly converts fibrinogen into fibrin. Thrombin itself is probably responsible for the autocatalytic mechanism of blood coagulation. How thrombin brings about "activation" of the "labile component" to "serum accelerator" has already been described. Thrombin also produces clumping and disintegration of platelets at the site of its formation; this has been shown both by direct and indirect experiments.[49] When platelets are lysed or "labilized," more thromboplastin precursor is liberated and an autocatalytic reaction is initiated.

It is obvious that such an arrangement is ideal for the prevention of bleeding. *In vivo*, the formation of thrombin is counteracted not only by the presence of natural anticoagulants, but

possibly even more by the washing effect of blood which pours out of the wound. Even if this washing effect is somewhat decreased by the vasoconstriction caused by liberation of the platelet vasoconstrictor principle, it would probably still interfere seriously with the normal initiation and maintenance of the autocatalytic phase of blood coagulation, this is effectively checked and directed. Some evidence is available to show that thrombin has a greater affinity for fibrinogen than for the antithrombic albumins. This circumstance assures that no

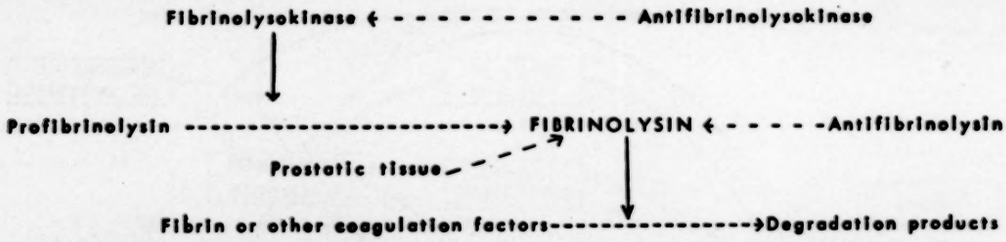

FIG. 9. The fibrinolytic system in human blood. Profibrinolysin (*proenzyme:* plasminogen; tryptogen; prolysin; lytic factor) found in plasma and serum is activated to fibrinolysin [*enzyme:* plasmin; tryptase; lysin (tissues)] by a fibrinolysokinase [*activator:* fibrinokinase; found in tissues (especially lungs and uterus)]. The action of kinase is probably inhibited or antagonized by a number of inhibitors present in plasma and serum (antifibrinolysokinase). The activity of active fibrinolysin is inhibited by antifibrinolysin (antiplasmin), also found in plasma and serum. Alternatively, a proteolytic enzyme (similar, but probably different from fibrinolysin) is produced by prostatic tissue and may be found occasionally in the circulating blood in disseminated prostatic carcinoma.

formation of a fibrin plug were not the thrombin formed at ever greater speed and in ever increasing amounts. The autocatalytic mechanism ("chain reaction") is, indeed, so effective that it may even compensate for a limited deficiency of single coagulation factors. Patients with prothrombin activity of plasma as low as 20 per cent of normal, with "labile component" activity as low as 25 per cent of normal and platelet counts of 60,000 to 70,000 cu. mm. can still present an apparently normal clotting mechanism and show good hemostatic control. On the other hand, such a process, if unchecked, could be very dangerous to life itself, without the influence of controlling mechanisms which are able to contain and finally to interrupt the autocatalytic formation of thrombin. The role of physiologic antithrombin is a predominant one among these mechanisms. By combining with thrombin (a property which is likely to be shared by many other substances in the albumin fraction of plasma) to form metathrombin, antithrombin removes a large amount of the enzyme from the circulation. In this, antithrombin (or antithrombins) is aided by the fibrin clot itself. This concept, first presented by Foá,[50] was experimentally proven by Wilson[51] and has been emphasized by other investigators.[52,53] Fibrin acts as a large sponge able to adsorb large amounts of thrombin, which is again released *slowly* when the clot retracts or is lysed. By removing thrombin, the key substance in the thrombin is neutralized until sufficient fibrin has been formed for good hemostatic control.

THE FIBRINOLYTIC SYSTEM

As the fibrinolytic system becomes better investigated, its complexity competes with that of the process of blood coagulation itself. (Fig. 9.) An inert proenzyme is found in Cohn's plasma fraction III-3 and in serum (profibrinolysin). It is water soluble and precipitated by 33 per cent saturation with $(NH_4)_2SO_4$, or acidification to pH 5.5. Profibrinolysin is converted to fibrinolysin by the activity of fibrinolysokinases. These are produced by bacteria (streptokinase) and, in mammals, are found in serum (in very small amounts) and in various tissues. The activator is a relatively heat labile substance, very complex in chemical structure and definitely different from thromboplastin. The activity of fibrinolysokinase is countered by an inhibitor (antifibrinolysokinase) which accompanies the activator in tissues and can also be found in serum. Active fibrinolysin is inhibited by antifibrinolysin, which combines with fibrinolysin according to definite stoichiometric proportions. Fibrinolysin cannot be identified with trypsin.

Activation of fibrinolysin and of the fibrinolysin/antifibrinolysin equilibrium is under the control of basic mechanisms in the economy of the body. Activation of fibrinolysin may be induced by "stress" and is one of the facets of

the so-called "alarm reaction." The pituitary-adrenocortical-splenic axis controls the activity of antifibrinolysin. According to Ungar and Damgaard[55] the inactivation of fibrinolysin by antifibrinolysin is regulated by ACTH and cortisone and by at least two splenic factors of opposing activity (splenin A and splenin B). The equilibrium of the fibrinolytic system is very well regulated, and tissue destruction of important degree or other comparable stimulus is necessary to induce activation of fibrinolysin.

Notwithstanding a large amount of work, many fundamental problems of the process of fibrinolysis remain unsolved. It is doubtful whether the fibrinolysin-antifibrinolysin equilibrium enters into the regulation of the plasma fibrinogen level. Also uncertain is the extent of activation of fibrinolysin which follows the normal coagulation process in man, and the role this mechanism plays in the disposal of the blood clot. Hemorrhagic diseases due to excessive fibrinolysis are gaining wider recognition and will be discussed later.

THE METABOLISM AND PHYSIOLOGIC ROLE OF THE VARIOUS COAGULATION FACTORS

Available evidence indicates that fibrinogen, prothrombin, stable and labile component and, possibly, antihemophilic globulin are produced by the liver. Many other organs and tissues may, of course, contribute to the synthesis of these proteins. Vitamin K and a nutritional factor present in brewers' yeast and liver extract (different from folic acid and vitamin B_{12}) are required for the synthesis of prothrombin and stable component.[56] This factor is also responsible for the macrocytosis of pernicious and other macrocytic anemias (protein synthesis factor). All conditions interfering with proper intake and absorption of vitamin K or protein synthesis factor may be responsible for the decreased rate of formation of these various coagulation agents.

From a practical point of view, particularly in connection with transfusion therapy in hemorrhagic diseases, it is important to have definite information on the survival time of the various coagulation factors and on the mechanism of their utilization. While fibrinogen and prothrombin in plasma and stable component in plasma and serum survive for long periods of time under certain conditions of temperature, blood and plasma must be given fresh and very shortly after collection to prevent deterioration and loss of activity of antihemophilic globulin and labile component. Lyophilization of plasma to a great extent prevents deterioration of all coagulation factors *in vitro*. By administering specially treated plasma and serum or crudely purified agents to patients with deficiency of a single coagulation factor, the "survival time" of that factor can be studied by serial determinations of concentration or activity. Fibrinogen survives as long as ninety-six hours or more; prothrombin disappears from the circulation in thirty-six to seventy-two hours after its administration. Labile and stable component are even more quickly utilized, since they disappear from the circulation in twelve to twenty-eight hours. Of antihemophilic globulin, 90 per cent is metabolized in twelve to fifteen hours. (Fig. 10.) Although these data are of great importance in directing therapy of conditions due to deficiency of the various coagulation factors, it should not be forgotten that from the clinical point of view administration of plasma or serum may favorably influence bleeding long after the administered factor has disappeared from the patient's circulation, as established by ordinary laboratory methods. Some paradoxical effects may also be observed. Patients with severe cirrhosis of the liver and clinical bleeding usually present, among other defects of the hemostatic mechanism, combined deficiency of prothrombin, stable and labile component. When serum (which contains little or no prothrombin and labile component) is given to these patients, considerable improvement of the bleeding manifestations may be observed, although the one-stage prothrombin time remains unmodified and only the concentration of stable component in plasma may temporarily rise. A highly theoretical explanation of this finding may be that the administration of "stable component" could allow complete utilization of the available prothrombin and labile component, and therefore influence favorably the hemostatic process.

Of considerable interest are a series of studies and hypotheses directed toward investigation of the possible role of various coagulation agents in the general economy of the body. The great excess of many of the clotting factors in the circulating blood and their rapid turnover suggest that they may play a role in body function other than blood clotting. This problem has been investigated particularly with respect to fibrinogen. This protein has some unspecified relation to immunologic mechanisms and phago-

cytosis, and certainly takes part in wound repair. Another possible important function of fibrinogen has been suggested recently, namely, that of a building stone of the hemapoietic tissue. This is suggested by a number of experimental[57] and clinical findings. Thus the reticulocytic crisis which follows treatment of full-blown tropical sprue is accompanied by a sudden drop in the total plasma protein level and particularly of fibrinogen.[58] Also, patients with polycythemia vera often present hypofibrinogenemia in the active stage of the disease. The level of fibrinogen rises following depression of the hematopoietic activity by myelo-suppressive agents like triethylene melanine.[59] All these and other facts suggest that fibrinogen may be useful for hematopoiesis and, possibly, a building stone for the synthesis of the protein moiety of hemoglobin.

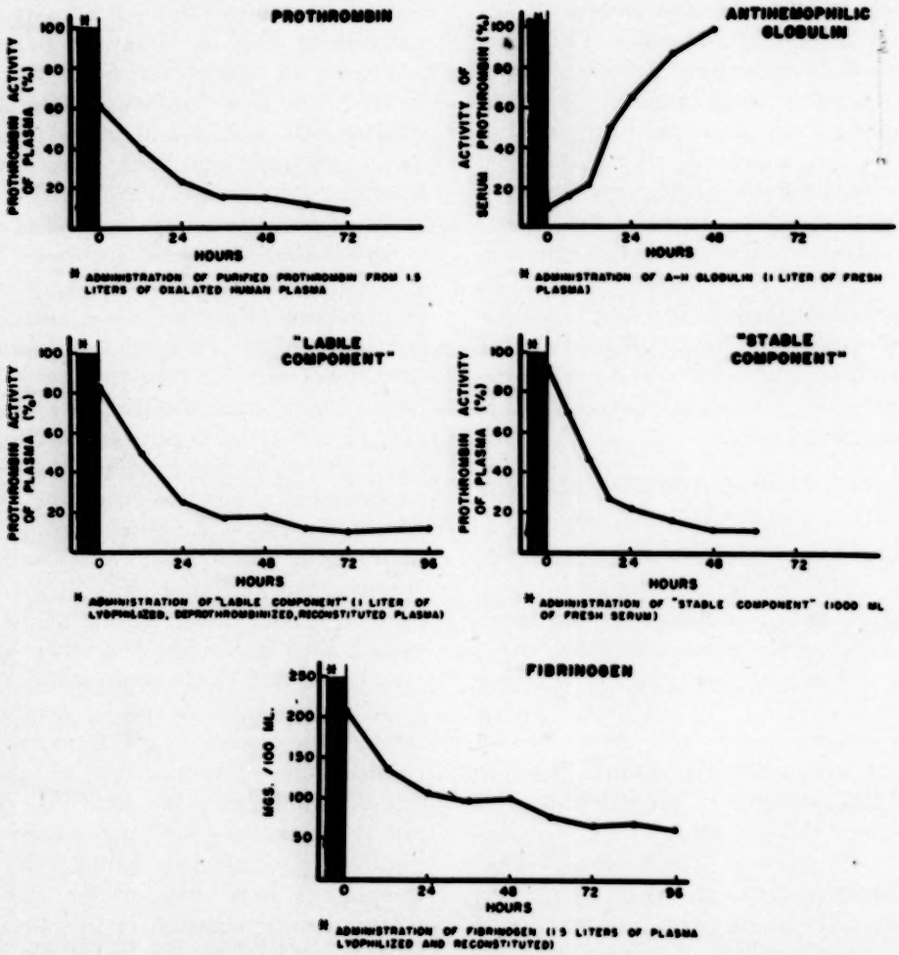

FIG. 10. The survival of various coagulation factors *in vivo*. Patients in whom these studies were performed had severe, apparently congenital deficiency of the specific agent investigated. Data on survival of prothrombin are partly influenced by the contemporary administration of "stable component."

ABNORMAL COAGULATION MECHANISMS IN HEMORRHAGIC DISEASES

Inadequacy of the normal blood coagulation process is due in most cases to one of three chief causes: (1) quantitative or qualitative (?) deficiencies in one or more of the various coagulation factors supplied by platelets and plasma; (2) the presence of excess circulating anticoagulants, which interfere with the normal coagulation mechanism; (3) destruction of the fibrin clot and circulating coagulation factors by increased lytic (fibrinolytic) activity of the plasma. While group (1) includes the hemorrhagic diseases most commonly encountered in

clinical practice, the importance of excess circulating anticoagulants and of fibrinolysis in the pathogenesis of bleeding disorders has been recognized more frequently in recent years.

No attempt will be made here to discuss the pathogenesis of hemorrhagic diseases due to quantitative or qualitative deficiencies of platelets and individual coagulation factors. Thrombocytopenia, hemophilia and diseases due to abnormalities of the factors taking part in the activation of prothrombin will be discussed in other sections of this Symposium. There are, however, a few concepts which should receive critical consideration. Caution should be exercised in evaluating the importance of limited depletion of coagulation factors in a bleeding patient. Platelets and coagulation factors are found in the circulating blood in amounts greatly exceeding the demands of normal hemostasis. When the capillary tree is intact, the activity of coagulation factors usually falls to very low "critical" levels before spontaneous bleeding occurs. This critical level may be as low as 20 to 30 per cent activity for plasma prothrombin and as low as 60 to 80 mg. per cent for fibrinogen, as previously mentioned. Bleeding may follow, however, with much higher values, if the capillaries are abnormal and capillary resistance is decreased.

The hemostatic defect is likely to be of a complex nature in the hemorrhagic tendency secondary to various diseases. The hemostatic defect in acute leukemia primarily reflects the severe thrombocytopenia, and the several aspects of this deficiency have been described previously. More complex is the hemostatic insufficiency in liver disease. In parenchymal liver disease the platelet count may be low and the plasma fibrinogen usually is low; the activity of prothrombin, labile and stable component is reduced, that of antihemophilic globulin may also be low. The capillaries, too, are often involved, as indicated by increased fragility (positive tourniquet test). In some cases depletion of coagulation factors may be further aggravated by increased fibrinolytic activity, since fibrinolysin may destroy many of the coagulation agents. The response of prothrombin[60] and stable component activity to administration of vitamin K is, in fact, a good index of liver function; that of labile component is not influenced by this therapy. A completely different picture (low activity of prothrombin and stable component promptly restored to normal by vitamin K, high antithrombin activity of plasma, normal or elevated plasma fibrinogen level) may be found in obstructive jaundice. This difference is often so striking that a "profile of hemorrhagic tests" can be usefully employed for the differential diagnosis of parenchymal and obstructive jaundice.[61,62] (Table VII.) In obstructive jaundice the capillary

TABLE VII

HEMOSTATIC DEFECT IN PARENCHYMAL LIVER DISEASE AND OBSTRUCTIVE JAUNDICE

	Parenchymal Liver Disease	Obstructive Jaundice
Platelet count	Normal or decreased	Normal
Bleeding time	Normal or prolonged	Usually prolonged
Capillary fragility	Increased	Increased *
Clot retraction	Normal or poor	Normal
Coagulation time (a) in glass tubes	Normal	Normal
(b) in Silicone tubes	Prolonged	Prolonged
Prothrombin activity (a) plasma	Decreased	Decreased *
(b) serum	Normal or high	Low
Serum/plasma prothrombin activity ratio	Normal or elevated	Normal
Labile component activity (a) plasma	Decreased	Normal
(b) serum	Elevated	Elevated
Serum/plasma labile component activity ratio	High	High
Activity of serum accelerator	Low	Low
Stable component activity	Low	Low *
Fibrinogen plasma level	Low	High
Fibrinolytic activity of plasma	High (at times)	Low
Antithrombin activity of plasma	Low	High

* Completely corrected by the administration of vitamin K, provided the liver is functionally normal.

fragility also is usually increased and is corrected by the administration of vitamin K through an unexplained mechanism.[63] In hemorrhagic disease of the newborn, prothrombin and stable component are both reduced; even in the normal newborn there is a moderate, combined deficiency of prothrombin and stable component[64] which is surprising since the activity of stable component is increased in maternal blood. These are only a few examples of the complex pathogenesis of hemorrhage in clinical conditions.

Circulating anticoagulants are being recognized in an increasing number of patients with severe bleeding tendency. In some instances the nature of the anticoagulant is unknown; in others, heparin or heparin-like substances are present in the circulating blood. In the first instance the anticoagulant develops in individuals receiving repeated transfusions over a number of years, as in hemophiliacs; spontaneously in patients with other diseases (tuberculosis, pemphigus, chronic glomerulonephritis, lupus erythematosus[65]), shortly after pregnancy or without any apparent cause. In all instances the anticoagulant is of similar nature and has similar properties: it is a gamma globulin resistant to storage and heat (65°C.), active over a wide range of pH, non-dialyzable (in practically all cases), not extractable with ether, not absorbed by gels, not affected by protamine, and only slightly if at all, and then temporarily, by massive blood and plasma transfusions. It can be clearly distinguished from the anticephalin or antithromboplastin of Tocantins,[67] excess of which, according to this author, would represent the fundamental coagulation defect in hemophilia.

Two types of disturbance of coagulation have been found to be due to the presence of such a circulating anticoagulant: (1) hemophilia-like disease, in which the activity of prothrombin is normal in plasma but the protein is very poorly utilized during clotting (very short prothrombin time of serum). The anticoagulant in this case probably prevents conversion of the plasma thromboplastic factor (antihemophilic globulin) to active thromboplastin; (2) hypoprothrombinemia-like disease, in which the prothrombin time of plasma is prolonged. The anticoagulant probably interferes with the conversion of prothrombin to thrombin. The mechanism of development of the anticoagulant is obscure, although many established facts suggest that it may be due to a process of isoimmunization.[66] These facts are: (1) anticoagulants of the type described may develop in hemophiliacs receiving multiple transfusions over a long period of time. The plasma and serum of these patients will at times show a positive precipitation test against normal plasma or purified antihemophilic globulin. The response of these individuals to transfusions of whole blood, plasma and antihemophilic globulin is extremely poor, suggesting that the injected globulin is inactivated or neutralized by the anticoagulant. (2) The anticoagulant has been detected in some patients shortly after termination of pregnancy (sensitization through placenta?). (3) The anticoagulant has been found in patients in whom other indications of isoimmunization are present.[65] One may even ask whether the increasing frequency with which excess anticoagulants are being detected may not be related to the more frequent use of transfusion therapy. It will be noted that some of these patients may recover spontaneously. Also, the acquired resistance to plasma in hemophiliacs may greatly decrease if blood and plasma are used parsimoniously in these patients.

In a second group of patients the circulating anticoagulant can be identified with heparin or heparin-like substances. Hyperheparinemia may *occasionally* develop in patients receiving massive doses of nitrogen mustards, x-ray and ionizing radiations. As mentioned, however, the presumptive hyperheparinemia of acute leukemia and thrombocytopenic purpura is, in effect, an expression of platelet deficiency. In extremely rare cases abnormalities of the plasma protein pattern may be responsible for hemorrhagic tendency. Thus, increase in α- and β-globulins has been shown to cause a disturbance in the fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin conversion (with a mild hemorrhagic tendency), which can be corrected by dilution of plasma.[68] One wonders whether excessive hyperglobulinemia (γ globulin) might not contribute to the bleeding tendency sometimes found in patients with multiple myeloma who show only minor thrombocytopenia and decreased resistance of the capillary wall.[69]

A complete breakdown of the coagulation mechanism may be due to fibrinolysis. Activation of fibrinolysis in humans is usually due to liberation of fibrinolysokinase from tissues, as in hemorrhage, shock, trauma, extensive surgery (especially of the lung[70]), etc. It may also occur

in and be responsible for the severe hemorrhagic diathesis of premature separation of the placenta.[71] Alternative explanations have been offered for the latter dramatic syndrome. The sudden hypofibrinogenemia and hypoprothrombinemia characteristic of the disease have been attributed to passage into the circulation of thromboplastic substances inducing intravascular clotting, hence utilization of fibrinogen and prothrombin;[72] or even to sudden failure of production of coagulation proteins by the liver. It may be of interest at this point to remark that lung and uterus are organs containing the greatest concentration of fibrinolysikinase activity. Excessive bleeding due to fibrinolysis ("fibrinolytic purpura") may also be found in leukemia, cancer of various organs,[73] etc. A special case seems to be disseminated carcinoma of the prostate, in which lysis is probably due to excessive production by the prostatic tissue of a proteolytic enzyme similar to but not identical with fibrinolysin.[74] This enzyme may be neutralized by the administration of a special tissue inhibitor[75] and is reduced, either in production or activity, by the administration of cortisone.[76] In chronic diseases, and especially in parenchymal liver disease,[77] fibrinolysis is occasionally observed. Fibrinolysis, by causing a total breakdown of the hemostatic mechanism, may be responsible for most severe hemorrhagic manifestations. The enzyme is known to digest not only fibrin but also fibrinogen and prothrombin. Other coagulation factors of protein nature (stable and labile component, antihemophilic globulin) are also attacked by the enzyme, as demonstrated by the extremely shortened survival of these proteins in the circulation of patients with high fibrinolytic activity.[78] The hemorrhagic diathesis which follows requires prompt and vigorous handling,[76] including administration of large volume of plasma, purified fibrinogen (fraction I) and, possibly, cortisone.

Recently, interest has been shown in the possible role of the fibrinolytic system in the pathogenesis of thromboembolism. It is known, for example, that antifibrinolysin activity may be increased in coronary thrombosis, thus theoretically inhibiting disposal of the clot by fibrinolysin. The same observation has occasionally been made in other thromboembolic conditions. However promising these findings may be, the few experimental and clinical observations available do not permit of any definite conclusion.

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REFERENCES

1. Clark, W. G. and Jacobs, E. Experimental nonthrombocytopenic purpura: a review of the Japanese literature with preliminary confirmatory report. *Blood*, 5: 320, 1950.
2. Spaet, T. H. Analytical review: vascular factors in the pathogenesis of hemorrhagic syndromes. *Blood*, 7: 641, 1952.
3. Stefanini, M. Recent advances in the theory of the normal mechanism of hemostasis. *Int. Rec. Med.*, 165: 431, 1952.
4. Campbell, E. W. Blood Research Laboratory, New England Center Hospital. Unpublished observations, 1952.
5. Allen, G. J. Protamine titration in hemorrhagic states. *J. Lab. & Clin. Med.*, 34: 473, 1949.
6. Fonio, A. Neuere Untersuchungen über die Physiologie der Thrombozyten, p. 523. Proc. III Int. Congress of the Int. Soc. of Hematology, Cambridge, August, 1950. New York, 1951. Grune & Stratton.
7. Stefanini, M., Salomon, L. and Perez, E. S. Thrombocytoasthenias: multiple syndromes due to qualitative platelet deficiency. *Proc. Nat. Meeting, Am. Fed. Clin. Research*, May 4, 1952.
8. Miale, J. B. The role of coagulase-globulin in blood coagulation and its thromboplastic action. *Am. J. Clin. Path.*, 22: 218, 1952.
9. Schulman, I. and Smith, C. H. Hemorrhagic disease in an infant due to deficiency of a previously undescribed clotting factor. *Blood*, 7: 794, 1952.
10. Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B. and Bates, G. Plasma thromboplastic component (PTC) deficiency: a new disease resembling hemophilia. *Proc. Soc. Exper. Biol. & Med.*, 79: 692, 1952.
11. Alexander, B., Goldstein, R. and Landwehr, G. The prothrombin conversion accelerator of serum (SPCA): its partial purification and its properties compared with serum Ac-globulin. *J. Clin. Investigation*, 29: 881, 1950.
12. Bordet, J. Réchèrches sur la coagulation du sang. Sérozyme et prosérozyme. *Compt. rend. Soc. de biol.*, 82: 896, 1919.
13. Quick, A. J. and Stefanini, M. The state of component A (prothrombin) in human blood; evidence that it is partly free and partly in an inactive or precursor form. *J. Lab. & Clin. Med.*, 34: 1203–1215, 1949.
14. Quick, A. J. and Stefanini, M. The chemical state of the calcium reacting in the coagulation of blood. *J. Gen. Physiol.*, 32: 191, 1948.
15. Stefanini, M. Antithrombin activity of stored plasma. *Am. J. Clin. Path.*, 18: 537, 1949.

16. Quick, A. J. and Stefanini, M. Effect of dicumarol on the concentration of the labile factor. *Proc. Soc. Exper. Biol. & Med.*, 72: 232, 1949.
17. Owren, P. A. La proconvertine. *Rév. d'hémat.*, 7: 147, 1952.
18. Alexander, B., Goldstein, R., Landwehr, G. and Cook, C. D. Congenital SPCA deficiency: a hitherto unrecognized coagulation defect with hemorrhage rectified by serum and serum fractions. *J. Clin. Investigation*, 30: 596–608, 1951.
19. Owren, P. A. Personal communication.
20. Stefanini, M. and Salomon, L. Blood Research Laboratory (New England Center Hospital). Unpublished observations, 1951–1952.
21. Ware, A. G., Guest, M. M. and Seegers, W. H. Fibrinogen: with special reference to its preparation and certain properties of the product. *Arch. Biochem.*, 13: 231, 1957.
22. Stefanini, M. and Crosby, W. H. Complementary correction of the defective coagulation mechanism of hemophilic and thrombocytopenic blood. *Proc. Soc. Exper. Biol. & Med.*, 73: 301, 1950.
23. Collingwood, B. J. and MacMahon, M. T. The anticoagulantsi n blood and serum. *J. Physiol.*, 45: 119, 1912.
24. Nolf, P. The coagulation of blood. *Medicine*, 17: 381–411, 1938.
25. Bordet, J. and Gengou, O. Sur le pouvoir coagulant du sérum. *Ann. Inst. Pasteur*, 18: 98, 1904.
26. Howell, W. H. The nature and action of the thromboplastic (zymoplastic) substance of the tissues. *Am. J. Physiol.*, 31: 1, 1912.
27. Quick, A. J. On the various properties of thromboplastin (aqueous tissue extracts). *Am. J. Physiol.*, 114: 282. 1936.
28. (*a*) Chargaff. E., Bendich. A. and Cohen, S. S. The thromboplastic protein: structure, properties, disintegration. *J. Biol. Chem.*, 156: 161, 1944. (*b*) Chargaff, E. The isolation of preparations of thromboplastic protein from human organs. *J. Biol. Chem.*, (*c*) Chargaff, E. and West, R. Biological significance of thromboplastic protein of blood. *J. Biol. Chem.*, 162: 189–197, 1946.
29. Patton, T. B., Ware, A. A. and Seegers, W. H. Clotting of plasma and silicone surfaces. *Blood*, 3: 656, 1948.
30. Shinowara, G. Y. Enzyme studies on human blood. xi. The isolation and characterization of thromboplastic cell and plasma components. *J. Lab. & Clin. Med.*, 38: 11–22, 1951.
31. Quick, A. J. Studies on the enigma of the hemostatic dysfunction of hemophilia. *Am. J. M. Sc.*, 214: 272–280, 1947.
32. Brinkhous, K. M. Clotting defect in hemophilia; deficiency in plasma factor required for platelet utilization. *Proc. Soc. Exper. Biol. & Med.*, 66: 117–120, 1947.
33. Quick, A. J. and Epstein, E. Thromboplastin activity in human blood. *J. of Appl. Physiol.*, 4: 840–847, 1952.
34. Seegers, W. H., McClaughry, R. I. and Fahey, J. L. Some properties of purified prothrombin and its activation with sodium citrate. *Blood*, 5: 421, 1950.
35. Koller, F., Loeliger, A. and Duckert, F. Experiments on a new clotting factor (clotting factor vii). *Acta haemat.*, 6: 1, 1951.
36. Mertz, E. T., Seegers, W. H. and Smith, H. P. Prothrombin, thromboplastin and thrombin: quantitative interrelationship. *Proc. Soc. Exper. Biol. & Med.*, 42: 604, 1939.
37. Stefanini, M. and Crosby, W. H. Utilization of the labile factor during normal and abnormal coagulation of blood. *Proc. Soc. Exper. Biol. & Med.*, 74: 370, 1950.
38. Alexander, B., Landwehr, G. and Goldstein, R. The labile factor of prothrombin conversion: its consumption in normal and abnormal blood coagulation. *Federation Proc.*, 9: 4, 1950.
39. Lewis, J. H. and Ferguson, J. H. Thrombin formation. I. The role of calcium, serum Ac-globulin and tissue thromboplastin. *J. Clin. Investigation*, 27: 778, 1948.
40. Morrison, P. R. and Scudder, C. L. Fibrin clot structure during clotting as observed in unsupported films under electron microscope. *Am. J. Physiol.*, 170: 147, 1952.
41. Ferry, J. D. and Morrison, P. R. The conversion of fibrinogen to fibrin under various conditions. *J. Am. Chem. Soc.*, 69: 388, 1947.
42. Laki, K. Transition of fibrinogen to fibrin. xvii Int. Phys. Congress, Oxford, 1947; abst. p. 373.
43. Mommaerts, W. F. H. M. On the nature of forces operating in blood clotting. *J. Gen. Physiol.*, 29: 103, 113, 1945.
44. Lyons, R. N. Thiol-vitamin K mechanism in the clotting of fibrinogen. *Australian J. Exper. Biol. & M. Sc.*, 23: 131, 1945.
45. Cummine, H. and Lyons, R. N. A study in intravascular thrombosis. *Brit. J. Surg.*, 35: 337, 1948.
46. Apitz, K. Ueber Profibrin. ii. Die Bildung von Profibrin bei Denaturzierung des Fibrinogens. *Ztschr. & d. ges. exper. Med.*, 102: 202, 1937.
47. Zucker, M. B. Platelet agglutination and vasoconstriction as factors in spontaneous hemostasis in normal, thrombocytopenic, heparinized and hypoprothrombinemic rats. *Am. J. Physiol.*, 148: 275, 1947.
48. Arthus, M. Etude sur la production de fibrinoferment dans le sang extrait de vaisseaux. *Compt. rend. Soc. de biol.*, 53: 1024, 1901.
49. Stefanini, M. Autocatalytic formation of thrombin in blood coagulation. *Acta med. Scandinav.*, 140: 290, 1951.
50. Foà, C. Sulle leggi d'azione della trombina. *Arch. Fisiol.*, 10: 479, 1910.
51. Wilson, S. J. Quantitative studies on antithrombin. *Arch. Int. Med.*, 69: 647, 1942.
52. Seegers, W. H. Multiple protein interactions as exhibited by the blood clotting mechanism. *J. Phys. & Colloid Chem.*, 51: 198, 1947.
53. Quick, A. J. and Favre-Gilly, J. Fibrin, a factor influencing the consumption of prothrombin in coagulation. *Am. J. Physiol.*, 158: 387, 1949.
54. MacFarlane, R. G. and Biggs, R. Observations on fibrinolysin; spontaneous activity associated with surgical operations, trauma, etc. *Lancet*, 2: 862, 1946.
55. Ungar, G. and Damgaard, E. Studies on the fibrinolysin-antifibrinolysin system in serum. i.

Action of the anterior pituitary, adrenal cortex and spleen. *J. Exper. Med.*, 93: 89, 1951.
56. Owren, P. A. Personal communication.
57. Whipple, G. H. and Robscheit-Robbins, F. S. Anemia and hypoproteinemia in dogs. Various proteins in diet show various patterns of blood protein production. Beef muscle, egg, lactoalbumin, fibrin, viscera and supplements. *J. Exper. Med.*, 94: 223, 1951.
58. Stefanini, M. Unpublished observations.
59. Stefanini, M., Chatterjea, J. B. and Dameshek, W. Is fibrinogen utilized for hematopoiesis in "active" polycythemia vera? (with a note on the pathogenesis of the hemorrhagic manifestations in the disease). Abstr. IVth Int. Congress, Int. Soc. of Hematol., Buenos Aires, 1952.
60. Stefanini, M. La sindrome emorragica dell'ittero meccanico e delle disfunzioni epatiche quale espressione della carenza di un complesso antiemorragico. *Arch. per le sc. med.*, 69: 177, 1940.
61. Harrington, W. J., Manheimer, R. H., Desforges, J. F., Minkel, H. P., Brow, C. B. and Stohlman, F. The bleeding tendency in hepatocellular and obstructive jaundice. *Bull. New England M. Center*, 12: 121, 1950.
62. Stefanini, M. The hemorrhagic diathesis in hepatocellular and obstructive jaundice. Proc., III Int. Congress, Int. Soc. of Hematol., page 484, Cambridge, August, 1950. New York, 1951. Grune & Stratton.
63. Stefanini, M. and Petrillo, E. Importanza del fattore umorale nella diatesi emorragica degli epatopazienti. *Geor. di clin. med.*, 28: 37, 1947.
64. Larrieu, M. J., Soulier, J. P. and Minkowski, A. Le sang du cordon ombilical: étude complète de sa coagulabilité comparaison avec le sang maternel. Centre Intern. de l'Enfance. *Etudes neo-natales*, 1: 1, 1952.
65. Conley, C. L. and Hartmann, R. C. A hemorrhagic disorder caused by circulating anticoagulant in patients with disseminated lupus erythematosus. (Abstr.) *J. Clin. Investigation*, 31: 621, 1952.
66. Dreskin, O. H. and Rosenthal, N. A hemophilia-like disease with prolonged coagulation time and a circulating anticoagulant. Report of a case in a female. *Blood*, 5: 46, 1950.
67. Pons, E. R. and de Torregrosa, M. V. Hemorrhagic diathesis due to a circulating anticoagulant. *Blood*, 7: 20, 1952.
68. Uehlnger, E. A special coagulation disturbance in dysproteinemia. *Helvet. med. acta*, 16: 508, 1949.
69. Waldenström, J. Three new cases of purpura hyperglobulinemica. A study in long-lasting benign increase in serum globulin. *Acta med. Scandinav., suppl.*, 266: 931, 1952.
70. Mathey, J., Daumet, P., Soulier, J. P., Le Bolloch, A. G. and Fayet, H. Hémorrhagies graves au cours d'interventions thoraciques par incoagulabilité sanguine due à la fibrinolyse. *Mem. Acad. de chir.*, 76: 977, 1950.
71. Moloney, W. C., Egan, W. J. and Gorman, A. J. Acquired afibrinogenemia in pregnancy. *New England J. Med.*, 240: 596, 1949.
72. Schneider, C. L. "Fibrin embolism" (disseminated intravascular coagulation) with defibrination as one of the end results during placenta abruptio. *Surg., Gynec. & Obst.*, 92: 27, 1951.
73. Ratnoff, O. D. Studies on a proteolytic enzyme in human plasma VII. A fatal hemorrhagic state associated with excessive plasma proteolytic activity in a patient undergoing surgery for carcinoma of the head of the pancreas. *J. Clin. Investigation*, 31: 521, 1952.
74. Tagnon, H. J., Whitmore, W. F. and Shulman, N. R. Fibrinolysis in metastatic cancer of the prostate. *Cancer*, 5: 9, 1952.
75. Tagnon, H. J., Schulman, P., Whitmore, W. F. and Kravitz, S. C. The hemorrhagic syndrome of metastatic prostatic cancer and its treatment. (Abst.) *J. Clin. Investigation*, 31: 666, 1952.
76. Stefanini, M. and Gendel, B. R. Blood Research Laboratory, New England Center Hospital.
77. Godpasture, E. W. Fibrinolysis in chronic hepatic insufficiency. *Bull., Johns Hopkins Hosp.*, 25: 330, 1914.
78. Feissly, R. Nouvelles études sur l'hémophilie; séparation des facteurs plasmatiques intervenant dans la formation de la thrombine. *Helvet. med. acta*, 8: 823, 1941.
79. Laki, K. The autocatalytic formation of thrombin and the clotting effect of hemophilic blood. *Stud. Inst. M. Chem., Univ. Szeged*, 3: 5, 1943.
80. Lewis, J. H., Tagnon, H. J., Davidson, C. S., Minot, G. R. and Taylor, F. H. L. Relation of certain fractions of plasma globulins to the coagulation defect in hemophilia. *Blood*, 1: 166, 1946.
81. Lenggenhager, K. Weitere Fortschritte in der Blutgerinningslehre, 2nd ed., Leipzig, Thieme. 1949.
82. Quick, A. J. On the constitution of prothrombin. *Am. J. Physiol.*, 140: 212, 1943.
83. Owren, P. A. Parahemophilia: hemorrhagic diathesis due to absence of a previously unknown clotting factor. *Lancet*, 1: 446, 1947.
84. Fantl, P. and Nance, M. Acceleration of thrombin formation by plasma component. *Nature, London*, 158: 708, 1946.
85. Quick, A. J. Congenital hypoprothrombinemia and pseudohypoprothrombinemia. *Lancet*, 2: 379, 1947.
86. Honorato, C. R. Plasmatic co-factor of thromboplastin; its adsorption, with prothrombin and fibrinogen, by alumina and tricalcium phosphate gels. *Am. J. Physiol.*, 150: 381, 1947.
87. Ware, A. G. and Seegers, W. H. Serum Ac-globulin; formation from plasma Ac-globulin; role in blood coagulation; partial purification; properties; and quantitative determination. *Am. J. Physiol.*, 152: 567, 1948.
88. Owren, P. A. The coagulation of blood. Investigations on a new clotting factor. *Acta med. Scandinav., suppl.*, 194: 1–327, 1947.
89. Milstone, J. H. Three-stage analysis of blood coagulation. *J. Gen. Physiol.*, 31: 301, 1948.
90. Stefanini, M. Analytical review: conversion factors and accelerators in the formation of thrombin. *Blood*, 6: 84, 1951.
91. Owren, P. A. The prothrombin activating com-

plex and its clinical significance. Proc. 3rd Congress, International Society of Hematology, page 379, Cambridge, August, 1950. New York, 1951. Grune & Stratton.

92. MacMillan, R. L. Observations on the mechanism of action of dicumarol. *Science*, 108: 416, 1948.
93. Owen, C. A., Jr. and Bollman, J. L. Prothrombin conversion factor of dicumarol plasma. *Proc. Soc. Exper. Biol. & Med.*, 67: 231, 1948.
94. Jacox, R. F. Studies on the activation of a serum "prothrombin-converting factor." *J. Clin. Investigation*, 28: 493, 1949.
95. Mann, F. D. and Hurn, M. M. Complex mechanisms of Quick prothrombin test and effect of dicumarol. *Am. J. Clin. Path.*, 20: 225, 1950.
96. Alexander, B., Goldstein, R. and Landwehr, G. The prothrombin conversion accelerator of serum (SPCA); its partial purification and its properties compared with serum Ac-globulin. *J. Clin. Investigation*, 29: 881, 1950.
97. Sørbye, Ø., Kruse, I. and Dam, H. The factor in Dicumarol plasma which accelerates the coagulation of plasma from vitamin K deficient chicks. *Acta chem. Scandinav.*, 4: 831, 1950.
98. Van Crevald, S. and Paulssen, M. M. P. Significance of clotting factors in blood platelets, in normal and pathological conditions. *Lancet*, 2: 242, 1951.
99. Ware, A. G., Fahey, J. L. and Seegers, W. H. Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. *Am. J. Physiol.*, 154: 140, 1948.
100. Owren, P. A. A quantitative one-stage method for the assay of prothrombin. *Scandinav. J. Clin. & Lab. Invest.*, 1: 81, 1949.
101. Stefanini, M. New one-stage procedures for the quantitative determination of prothrombin and labile factor. *Am. J. Clin. Path.*, 20: 233, 1950.
102. Stefanini, M. Activation of plasma labile factor in disease. *Lancet*, 1: 606, 1950.
103. de Vries, A., Alexander, B. and Goldstein, R. A factor in serum which accelerates the conversion of prothrombin to thrombin I. Its determination and some physiologic and biochemical properties. *Blood*, 4: 247, 1949.
104. Quick, A. J. and Stefanini, M. The concentration of component A in blood, its assay and relation to the labile factor. *J. Lab. & Clin. Med.*, 34: 973, 1949.

Conference on Therapy

Treatment of Cough

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and the New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. MCKEEN CATTELL: The treatment of cough is the topic of the conference today. We all know that cough presents a very frequent therapeutic problem. The methods of treatment are not altogether free of controversy. The discussion today, with the participation of the audience, should survey the common grounds as well as the areas of disagreement.

Dr. Lansdown, who has given considerable thought to this problem, will make the opening remarks.

DR. FRANCES S. LANSDOWN: I have put on the blackboard an outline of cough problems which has helped me in dealing with them as they occur in patients. It is based on the site of origin of the trouble causing cough in the respiratory structures, going from above downward.

Before proceeding to the specific states in which the treatment of cough is the main problem, I should like to summarize the various measures that are used. I will postpone to the end some remarks on codeine and morphine.

A large number of drugs are used in cough: various salts, terpenes, creosote and other agents. These are used alone or in combination with syrups and flavoring agents. There is a vast number of combinations among the cough remedies of commerce. They increase or decrease secretions. They thin them down, making it easier to raise sputum. Counterirritants, steam inhalations, warmth, hot and cold drinks, abdominal binders and drainage by postural and bronchoscopic methods are used.

Education of the patient regarding the function of the cough and the best method for controlling it should perhaps head the list. Patients can be made to understand that sputum in the cup is preferable to the same material in their lungs. Many have the idea that the more noise they make the more effective the cough. They fail to realize that constant hacking and hawking only causes further irritation of the tracheobronchial mucosa, thus propagating a vicious cycle. Most patients can learn to empty the respiratory tract with quiet, forceful expirations or by postural drainage, thus lengthening the intervals between paroxysms of coughing. Advice on this point is especially helpful to those with severe cough at mealtime, which may cause vomiting. If they clear the lungs before meals, they eat in comfort. The same applies to nocturnal cough; if they drain the lungs at bedtime, they are apt to go through the night asleep without interruption and without medication. Working out a suitable regimen with the patient is very time-consuming but the results pay high dividends in satisfaction and permanence.

There are several useful facts which one should elicit before one proceeds to treat cough. First, there is the source of the cough. I do not refer to the site of origin of the reflex because this is usually in the major bronchi or trachea. The cough starts off when the material hits the sides of these passages. I refer to the actual source of the secretions. Then there is the question of the degree to which it disturbs the patient or his neighbors. We have probably all had coughs in association with colds which are loose, productive and comfortable. They elicit sympathy from our friends but they do not disturb us much. There seems to be no special point in treating these.

The time of the day when the cough occurs or when it is most troublesome is useful information for the diagnosis. For example, the cough from tuberculosis and bronchiectasis is usually worse in the morning while that from sinusitis comes on when the patient lies down at night. This information, furthermore, provides a lead as to when it is best to treat the patient or at what time of the day the most intensive treatment should be applied. For example, if the patient raises sputum with little trouble during

the day time but is kept awake at night by the cough, it may prove helpful to suppress the cough at night.

The amount of sputum that is secreted compared with the amount that is expelled supplies important information. For example, old and debilitated patients in terminal illnesses may secrete a huge volume of material but are unable to expel it. It is in this group of cases that I feel justified in using the full depressant doses of codeine and morphine, using them with the full knowledge that life may be shortened but the last days are being made more comfortable.

Then there is the type of sputum. For example, if it is tenacious and difficult to bring up, it would prove helpful to employ measures to thin it down rather than to suppress it. Finally, there are facts which the patient may have discovered about his cough which may provide the physician with useful information in treating him.

We may now pass on to the special treatments for cough of various origins. First, there is the cough which arises from the secretions in the sinuses. These patients are usually helped by warm, moist air. If they are put to bed in a room at constant temperature, especially if it is damp, they often cease to cough. If not, local treatment of the sinuses with vasoconstrictors is helpful, more so than opiates, to suppress the cough. I question the advisability of trying to suppress the cough from sinusitis for this allows the purulent matter to drain down into the respiratory tract. A trick we have applied with advantage in the nurses' infirmary is that of using ephedrine every four hours during the day. The patient can apply it himself. He lies across the bed with the head and shoulders off the bed and the nose pointed straight up to the ceiling. Both nostrils are filled to overflow with 0.25 per cent solution of ephedrine. He lies there breathing through the mouth for two minutes by the watch. This provides an opportunity for soaking the membranes around the ostia of the sinuses. Very often this may ease the cough sufficiently to make other treatment unnecessary.

In the case of cough originating in the trachea there may be a foreign body which calls for removal. Tracheitis, which usually means infection, presents one of the most stubborn problems in the treatment of cough. If one must treat the patient in the ambulant state, codeine is probably the only measure that will do any good. But if the patient is confined to bed, steam inhalation usually brings the cough under control. In this connection it is better to use the plan of keeping the steam kettle or the little inhaler going under the nose constantly throughout the day than the plan by which the head is placed over a bowl of steam for twenty minutes every four hours. Constant temperature is one of the most important factors.

Cough may arise from any one of several diseases involving the major bronchi. In the case of a foreign body correction may be simply a matter of its removal. In the case of pressure by nodes or aneurysm one applies whatever method is effective against these. For tumors of the bronchus the essential treatment is, of course, operative, if that proves to be possible. Codeine or morphine provide some relief. The measures used in tracheitis also apply to bronchitis. The counterirritant is an old-fashioned remedy but it may be quite helpful. Bronchiectasis presents a chronic disease with cough in the treatment of which education of the patient plays a very important part. When sufficient secretions accumulate, the patient begins to cough. One can work out a regimen of postural drainage at indicated hours of the day which will restore a fairly normal life to one whose social life is ruined by constant coughing. A decisive factor is the discovery of the correct posture which insures the most effective drainage. Whether it is in the home or in the hospital, it is not enough merely to prescribe postural drainage. What the posture shall be has to be determined in each case. Then the nurse and patient must receive specific instructions.

Cough of bronchiolar origin may be associated with asthma and come in paroxysms, or with spasm secondary to emphysema, in which case it is not so apt to be paroxysmal. Epinephrine and other bronchodilators provide relief. Vaponefrin is a popular preparation for this purpose. It is used with a glass nebulizer by inhalation and patients carry it about with them for use when the need arises.

For cough having its origin in the lungs, as in the exudative types of pneumonia, for example, those due to the pneumococcus, rest in bed, specific treatment for the pneumonia, keeping the patient warm, steam inhalations and small doses of codeine bring the symptom under control. Cough in the suppurative types of pneumonia, on the other hand, presents a different problem. This may be a chronic disease

and the patient has to learn to live with it. Bronchoscopic drainage is used, although I am inclined to question its value since the bronchoscope rarely reaches the seat of the trouble.

In tuberculosis patients also have to learn to live with their cough problem. Those in sanitaria learn by themselves or from other patients that a drink of hot milk or coffee in the morning greatly facilitates the expulsion of the material which accumulates during the night.

Patients with chronic emphysema are wet, so to speak, all the time. The secretion is at the bottom of their lungs. They cough and spit constantly. Some raise clear and mucoid material, although it often becomes purulent in the winter. Treatment in these instances is also very difficult. Stimulant expectorants appear to be most helpful. These people drink buckets of elixir terpin hydrate. Abdominal binders sometimes help since they raise the diaphragm and provide resistance against which they may cough. In these cases, also, there is need for educating the patient in the use of the cough most effectively.

Before concluding I would like to say a word about codeine. It is a common practice in the treatment of cough to prescribe codeine and let it go at that; and if a dose of 15 mg. is ineffectual, it is increased to 30 or even 60 mg. It is possible to suppress any cough by huge amounts of codeine but no end of damage may result. For example, infected material from a tuberculous cavity may spill over to the adjacent bronchi, causing a spread of the disease, or a lung abscess may fill up and break through the pleura causing a bronchopleural fistula and emphysema. A survey published in Supplement No. 158 of the U. S. Public Health Reports indicates that addiction to codeine is not as rare an occurrence as many people think. It describes several established cases of codeine addiction which had their origin in therapeutic amounts given over a protracted period of time. What I say about codeine applies to morphine when given in one-fifth the dose. Their advantages and disadvantages are similar, although there may be some differences in their side actions. I don't wish to imply that opiates should not be used in cough, for they are of great value. It is their indiscriminate and thoughtless use that is in need of more attention.

For some reason the smallest tablet of codeine that is dispensed in the hospital here contains 15 mg., and that which is most commonly used is one containing 30 mg. These doses seem to me unnecessarily large. For most cases of cough the advantage of a large dose over a small one lies chiefly in a more prolonged action. The depressant effect of 30 mg. of codeine on the cough mechanism is not substantially greater than that of 15 mg. It is only with the much larger doses that the effect becomes conspicuously more marked, and it is with these that one approaches the danger of suppressing the cough. I prefer to use doses of 10 mg. every two hours rather than larger doses at longer intervals. One teaspoonful, or 4 cc., of the elixir terpin hydrate with codeine of the National Formulary, a preparation which is commonly used for cough, contains only 8 mg. of codeine. This amount of codeine seems to be effective. It is doubtful that the elixir terpin hydrate in the teaspoonful exerts any substantial effect. In the U. S. Public Health Report to which I referred the result of a survey made at a large sanitarium, on 475 patients with troublesome cough, is included. Tablets containing 10 mg. of codeine were made up. The staff were asked to prescribe the dose of 10 mg. but were allowed to increase the dose if necessary. Up to the time the study was made 30 mg. was the smallest dose of codeine dispensed. It was found that only twenty-one of the 475 patients required codeine in doses larger than 10 mg. and of these only three required the doses of 30 mg. The study showed that any cough that would not respond to 100 mg. could not be relieved by three times that dose. The author concluded: "As the result of this study, smaller dosages of codeine are being administered at shorter intervals than previously. This probably means a better understanding of cough control, and if, as seems probable, patients are just as comfortable as formerly, the intangible saving through avoiding the side action of a narcotic is incalculable." He then adds that the use of narcotics in cough control is unnecessary in the large majority of patients suffering from tuberculosis. I believe this has been a common experience among those working in sanitoria who have taken the time to study the problem; and if it is true in tuberculosis, it is certainly true in coughs from other causes.

DR. CATTELL: Dr. Muschenheim, would you care to comment at this point?

DR. CARL MUSCHENHEIM: While it is a fact that this conference was planned to deal with ways and means of controlling cough, it may

be worth while to be reminded that cough is a physiologic mechanism which does not always have to be treated, and that there are sometimes urgent indications to do the reverse and promote cough. I venture the opinion that there have been more deaths from failure to cough than from coughing. The symptom cough is a source of important information in medical practice. The fact remains, however, that it may be a distressing symptom, painful and exhausting. When it is especially violent, it may cause damage to the lungs or to the thoracic cage. Fracture of a rib from coughing is not especially rare. In the endeavor to control cough I believe it is more effective to treat the cause of the cough than the symptom itself. The causes are so numerous and diverse, however, that I doubt we can cover more than a small number of them in this conference, and Dr. Lansdown has already done so. I hope, however, that the discussion will throw light not only on the question of how and when to treat a cough but also when not to treat it and, further, how best to promote cough when there is need for it.

I might amplify a few of Dr. Lansdown's remarks, especially in relation to postural drainage in suppurative diseases of the lung. In these, mechanical measures are far and away more important than pharmacologic aids. A contribution to the method of postural drainage was made in this hospital by Dr. Forkner and Dr. Timpanelli some years ago which, in my opinion, has not received the attention it deserves. The principle is to arrange the bed so that the patient with severe bronchiectasis, particularly during exacerbations with complicating suppurative pneumonitis, is maintained in a position favoring postural drainage constantly, even during the night. It can be done in several ways, namely, by raising the foot of the bed producing an inclination of 15 to 30 degrees, or by building it up in the middle producing a jackknife position so as to prevent all the blood running to the head. Patients tolerate this for twenty-four-hour periods. This technic, I believe, has vastly improved spontaneous healing of lung abscess in this hospital in the past four or five years. Only about 30 per cent of the patients with lung abscess used to heal when treated with conservative measures but in the recent years in which this method has been used the situation has been substantially reversed; we have not had to resort to surgical drainage in more than about 30 per cent of cases of acute lung abscess. In chronic bronchiectasis in which the sputum was abundant and so foul that to be in the same room with the patient was almost intolerable, this treatment has reduced the sputum to a few centimeters a day and has eliminated the foul odor.

There is another point to which I should like to refer. It is the value of bed rest. Bed rest has come in for a good deal of criticism recently but I think that these views have tended to obscure some of its virtues. In patients with tuberculosis cough diminishes very promptly with bed rest alone. It is associated with improvement in other ways but there is the striking fact that in the patient who has been coughing incessantly when he was up and about, cough and expectoration lessens fairly promptly and long before the cavity is closed, when he is put at complete bed rest.

Finally, I should like to hear a little more about cough mixtures. Dr. Lansdown did not say much about them. What are the special virtues of the ones we use? Do all kinds of cough respond equally well to one drug or mixture? Many of the mixtures which were popular years ago have fallen into discard. Now it is common practice to use codeine alone. Among the mixtures elixir terpin hydrate seems to be most popular. I looked up the action of terpin hydrate in several books on pharmacology and I discovered a want of agreement on the nature of its action as an expectorant. I wonder if Dr. Gold would tell us how it really does act. I would be interested in knowing what is to be expected from some of the other drugs which pharmacologists list as expectorants. I have not been impressed with any substantial benefit from any of them, with the exception of elixir terpin hydrate with codeine, which sometimes relieves a cough miraculously. Only yesterday I saw a patient to whose daughter I had given a prescription for the elixir terpin hydrate with codeine for a cough associated with a mild cold. I discovered that the mixture was passed along to other members of the family, to the cousins, sisters and aunts. Everyone in that group found that it "cured" their cough in a few days. We have all probably had similar experiences with this or other favorites. Some patients express the firm belief that codeine in a liquid vehicle is more effective than a tablet of codeine. I am not certain that the preference represents a pharmacologic difference.

I want to say a word or two about bronchitis.

As the result of the intensive search for the more serious causes of pulmonary symptoms, many have taken the position that there is no such thing as simple bronchitis. I have been told by physicians that their teachers in the medical school expressed their position in this way: If a patient has a cough, don't make a diagnosis of bronchitis but proceed to find the cause of the cough. I do not share that opinion. I believe that simple bronchitis is probably the most common cause of cough, far more frequent than tuberculosis, bronchiectasis or lung abscess.

DR. CATTELL: Dr. Gold, would you like to say something about expectorants?

DR. HARRY GOLD: Yes, the first point I should like to make about expectorants is to stress the desirability of abandoning the term. It is an obsolete term applied to cough remedies. I doubt that it ever had a clear meaning, and in these days when so much effort is put into rationalizing therapeutics this term places obstacles in the way of clear thinking on the subject of cough and how to treat it.

One of the foremost textbooks on pharmacology includes a chapter on expectorants. It defines them as drugs which assist in the removal of exudate from the respiratory tree. It then proceeds to classify them in the conventional manner as sedative, stimulant and anodyne expectorants, the anodyne expectorants referring to opiates which depress the cough mechanism by a central action. This is strange logic.

VISITOR: What would you have in its place?

DR. GOLD: A chapter on cough remedies would be a good substitute.

INTERN: Is there such a thing as a specific cough remedy?

DR. GOLD: I think we may speak of a specific cough medicine in a certain sense. It may be best to use an example to explain the point. Consider the case of a sixty year old woman with hypertensive and arteriosclerotic heart disease. When she lies down at night, she begins to cough. She has to sit up and after some minutes the cough subsides. When she receives enough digitalis and mercuhydrin, her cough problem is brought under complete control. Although the digitalis and mercuhydrin abolished the cough in a most dramatic fashion, it would not add to our knowledge to classify these as potent cough remedies. They control congestive failure, and in congestive failure the sole or presenting symptom is sometimes a stubborn cough.

I think it is well to confine the term cough remedy in a specific sense to a drug which acts to raise the threshold of the cough "center" in the central nervous system, or acts peripherally in the respiratory tract to reduce the impulses which pass to the center, or to a mixture which combines both actions.

STUDENT: How does the specific peripherally acting cough agent act? What does it do?

DR. GOLD: Most often it probably produces a favorable change in the respiratory secretions. Let us see how that can take place. If one analyzes the conventional reflex involuntary cough situation, the events can be seen to fall into a certain pattern. Each paroxysm is composed of a volley of coughs followed with a free interval. The interval varies in duration. The patient may have a volley of coughing every few minutes, or once in several hours of the day. Each blast may be mild or severe. The number of blasts may be two or three, or twenty or thirty in the length of a volley. Cough medicines may alter any phase of a paroxysm. A centrally acting medicine which raises the threshold of the cough center makes it necessary to build up a stronger stimulus before the trigger for a paroxysm of coughing is released. For example, if, in a particular case, the trigger is irritating mucopus in a bronchiectatic sac which fills sufficiently to exceed the threshold within about two hours so that the patient has a bout of coughing at intervals of approximately two hours during the day, the centrally acting cough remedy may cause what the patient refers to as improvement by reducing the number of coughing bouts and prolonging the intervals between them from perhaps two to four or five hours now required to fill the sac or distend it sufficiently to build up the necessary stimulus. The patient may report that he expels more material with each bout of coughing and that he gets more rest because the number of coughing paroxysms have been reduced from perhaps ten or fifteen to three or four during the day. This is especially welcome if the change refers to a pattern of cough that is most troublesome at night.

The term, expectorant, may be confined to the peripherally acting cough medicine. It is most often an irritant which acts on the respiratory mucous membrane directly or reflexly to increase the secretions. The increase in the secretions is apt to make them more alkaline and the rise in pH renders the mucous thinner and less

viscid. These factors alone or in combination protect dry mucous membranes against irritant particles and help to wash away adherent irritant mucopurulent plaques with a minimum of effort in terms of the severity and number of coughing blasts. The patient may report the cough as "easier." An analysis may show that the cycles recur as frequently as before but the number of coughs in a volley may be reduced, for example, from fifty to ten. Since long volleys and violent blasts tend, in themselves, to irritate the respiratory passages and promote the continuation of the cough in a vicious cycle, the action of the expectorant may also have the indirect effect of lengthening intervals between paroxysms of coughing.

A simple upper respiratory infection often presents cough as the dominant symptom. Through severe blasts and long volleys the cough produces sufficient irritation to sustain itself through a chain reaction long after the primary condition is gone. This is the kind in which prolonging the interval between volleys by a centrally acting cough medicine or reducing the number and severity of the blasts in each volley by an expectorant produces the extraordinary spectacle of a cough of long duration "cured" by a few doses of cough medicine. This would explain Dr. Muschenheim's experience with the magic cough cure which his patient passed on to all the members of the family.

DR. CATTELL: Dr. Muschenheim raised the question as to whether one cough medicine might be better than another in certain conditions. Have you anything to say about that?

DR. GOLD: Dr. Muschenheim touched on a very interesting point there. I have often put this question in relation to cough: What cough medicine do you commonly prescribe? The answer has almost invariably been: It depends on the kind of cough, whether it is a dry or a wet cough. If it is wet, we don't use the opiates; and if it is a dry cough, we use expectorants with or without opiates. This viewpoint has a logical appearance but I believe it is an oversimplification of the problem and that there may be, in fact, nothing in it at all. There are the very serious cough problems requiring postural or surgical drainage or other special devices for bringing them under control but for the great majority of cases in which a cough medicine is indicated I believe that whether the cough is wet or dry is a matter of indifference in the selection of a cough remedy. Opiates may be used in both of them. If a cough is productive, or so-called wet, it is obviously undesirable to use opiates too freely, but smaller doses which raise the threshold so that more secretion may have to accumulate before the cough reflex is activated are apt to prove useful.

Among the opium group I believe that morphine is much more effective than codeine. The cough center is so sensitive to morphine that minute doses usually suffice, doses which often produce no side effects. To produce similar results on the cough with codeine often requires enough codeine to produce side actions, particularly constipation.

At this point I should like to refer to a remark which Dr. Lansdown made earlier, namely, that it is possible to suppress any cough by huge amounts of codeine. I should like to raise the question whether it is not frequently impossible to suppress cough with any subnarcotic dose of any of the opiates. I believe that the response of the cough mechanism, like that of the pain mechanism, has a ceiling and that beyond a particular degree of action by the opiates it is not possible to produce appreciably greater effects.

VISITOR: I wonder if, for practical purposes, Dr. Gold would write out a sample prescription for a cough remedy including morphine and a good expectorant?

DR. GOLD: I wish you had not used the adjective "good" to describe the expectorant which I would put into a cough mixture. We have favored ones and the basis for the favoritism is usage and habit. There is, of course, the matter of compatibility in mixtures, and one has to avoid an incompatibility. Of this point I am certain, that my use of any particular expectorant has never been based on any evidence that it was more effective than another. I know of no evidence that can be used for this purpose.

Now back to the specific question. Here is the cough mixture I would prescribe:

℞

Morphine sulfate	0.03
Elixir terpin hydrate to make	60.00

Mix

Sig: 1 teaspoonful every 4 hours

Each teaspoonful contains $\frac{1}{30}$ gr. or 2 mg. of morphine sulfate; and if the patient takes four doses a day, he will have received 8 mg. of morphine. The interval between doses should

be worked out for each patient individually. The return of the cough is a good guide, and this will show the need for a dose every two hours or it will show that six or eight hours suffice. A period of one or two days with this medication should be sufficient to establish its utility in the particular case. There is not enough morphine in the whole bottle of 2 ounces to involve the risk of addiction, and if the patient were to take a notion to swallow the whole bottleful at one time, there is no risk of poisoning. There is only a total of ½ gr. or 30 mg. of morphine in the whole mixture. I believe it was the morphine which supplied the adequacy to the old time brown mixture and Stokes' expectorant which were once very popular cough remedies, even though a teaspoonful contained about only 0.25 mg. of morphine.

DR. MUSCHENHEIM: While morphine is very effective against cough, it is worth emphasizing that it depresses the respiration and should be used with great caution. I doubt whether it should ever be used in a case of hemoptysis. It does indeed reduce the amount of bleeding but there is danger in suppressing the elimination of the blood and clots. In tuberculosis, particularly, morphine may cause spread of the disease and development of the pneumonic type of tuberculosis.

DR. GOLD: I think it is quite proper to warn against the dangers of morphine, the fact that it can depress respiration and produce more depression of the cough reflex than is desirable. But at the same time it would seem wise to call attention to the fact that these excesses are matters of dosage. By appropriate adjustment of the dose one can secure as much or as little action of morphine on the cough mechanism as appears to be desirable. It is, therefore, inaccurate to refer to morphine as indicated in one condition and contraindicated in another. If it is the objective to raise the threshold of the cough center, morphine is the most effective drug for the purpose, and the amount of depression of the cough center is merely a matter of dosage.

DR. MARY LOVELESS: How about the iodides in bronchial asthma? Do they not have some value in controlling the cough of asthma?

DR. GOLD: That question comes up frequently. The iodides are useful expectorants. Most expectorants which are put into cough remedies are emetics. They produce gastric irritation. They may cause nausea and, in larger doses, vomiting. The earliest action of an emetic is that of increasing secretions. If it is taken by mouth, the irritation in the stomach not only causes increase of secretions in the stomach but, also reflexly increases secretions in the respiratory tract. This applies to such expectorants as terpin hydrate, syrup of squills, antimony and potassium tartrate, and ammonium chloride. Such materials reflexly excite secretions in the respiratory passages through an aromatic or penetrating odor, bitter or burning taste, or nauseant action. In the case of the iodides there may be an additional mechanism resulting from the excretion of the iodides through the mucous membranes of the respiratory tract. This action is particularly prominent after very large doses of the saturated solution of potassium iodide. These give rise to symptoms of coryza, often referred to as symptoms of iodism.

DR. CATTELL: Could we have some of your thoughts on the treatment of cough, Dr. Guion?

DR. CONNIE M. GUION: I might mention a few points which stand out particularly in my mind, since most of the measures have already been discussed by others. There has been no reference to cough as a means of spreading disease. I think this is an important matter. In a cough the glottis is opened and the contents of the respiratory tube are forcibly expelled at the rate of 150 to 160 feet per second. This indicates the importance of wearing a mask under the proper conditions. There is also the danger of coughing into one's hand, as a means of passing infection on at the next doorknob or with the next handshake. In acute pharyngitis the disagreeable hacking cough may be controlled by gargling with a solution of normal saline to each glassful of which there is added a half teaspoonful of bicarbonate of soda and a tablet of 0.3 gm. of aspirin. In the more severe forms which give rise to blood-stained sputum a spray of 1 per cent butyn sulfate or pontocaine is useful, although one must remember that these are toxic agents. One should avoid using so much as to cause numbness of the throat. Among the opiates I prefer dilaudid because it is less likely to produce constipation, drowsiness and nausea. In the case of codeine I use 30 mg. as the initial dose and follow this by 8 mg. every two hours. It is my experience that these doses, while decreasing the cough reflex, are not sufficient to abolish it. I should like to emphasize Dr.

Lansdown's remarks on steam inhalations. They are extremely important in cough. An endeavor is made to maintain a concentration of about 65 per cent in the atmosphere in which the patient breathes. Most of the numerous electrical devices for steam inhalation are unsatisfactory and some are dangerous. The small units may stop up and explode. They often burn the medication and such a material as burned benzoin is very irritating. I prefer a large tin pan on a hot plate, one which will produce a continuous flow of steam during the whole twenty-four hours. Some type of fragrance may be added to the steam, such as the compound tincture of benzoin, oil of pine or oil of turpentine. I doubt that these materials add much to the therapeutic value of the steam.

Reference has already been made to the use of counterirritants in the treatment of cough. I think it is an important measure and is especially useful in the cough of dry pleurisy. For this purpose I usually make use of the mustard plaster or a large flaxseed poultice; the poultice is put on as a jacket and kept warm with a hot water bag. You are probably all familiar with the practice of painting the skin with tincture of benzoin as a protection against the plaster if the patient's chest is to be strapped.

One of the major remedies against the cough associated with acute asthma is the intravenous injection of aminophylline. The dose is 0.24 gm. injected very slowly and repeated every four to six hours if there is need for it. For this purpose epinephrine is also very useful, either in the form of a spray or an injection of 0.3 to 0.5 cc. of the 1:1000 solution subcutaneously. The difficulty there is the tendency for epinephrine fastness or epinephrine addiction to develop.

The cough from atelectasis is not a common encounter but it presents a very important problem when it does occur, as it does most often postoperatively or after hemoptysis. Pounding the patient on the back from the base of the lung to the apex is an effective measure. I have seen members of our Department of Surgery apply it with great skill.

The cough of patients with emphysema and fibrosis presents one of the most difficult problems. I may emphasize Dr. Lansdown's suggestion of education of the patient to live within the limits of his respiratory reserve as the most important measure. Bronchiectasis and lung abscess, both conditions in which troublesome cough is an outstanding symptom, are to a large extent surgical problems; but when for a period medical treatment is necessary for one reason or another, I have found the regular schedule of steam inhalations the most efficacious measure.

DR. CATTELL: Dr. Levine of the Pediatrics Department is here today. Perhaps he might be willing to say a few words about the treatment of cough in children, especially in instances in which the problems of children and adults differ.

DR. MILTON I. LEVINE: Children and adults are in many respects alike in the cough problems which they present but there are sufficient differences to warrant special attention to the cough problems of children. Several measures which are used with eminent success in adults are not very useful in children either because of differences in reactions or because of special difficulties which children place in the way of successful application of the measures. We try to avoid painting the throat in youngsters. We also try to avoid ice collars in children; they sometimes struggle so violently with ice collars that it is better to take them off. Putting packs on the chest presents an unusually difficult problem in children and we avoid that when we can. In regard to medicines, pediatricians tend to concentrate on things which have a pleasant taste. I am in the habit of tasting everything I prescribe for children. One of the first things I do when I have a visit from a detail man is to taste the mixtures he advocates. That gives me an idea as to whether the child will take the medicine without a fuss. I have a notion that most pediatricians follow the same plan. The pediatrician has to remain in the good graces of his patients.

The number of drugs we use in treating children is quite small. Ammonium chloride is an expectorant commonly used by pediatricians, in the form of a mixture containing 0.3 to 0.5 gm. to the teaspoonful of syrup of wild cherry. Another popular one is syrup of ipecac in doses of ¼ teaspoonful every two or three hours. Codeine is added if the cough is too wracking, as is sometimes the case in whooping cough.

We make a great deal of use of steam inhalation in treating the cough of babies. The popular vaporizers are undoubtedly a source of danger. Not many days elapse in my own experience and in that of my colleagues without an account of one or more children sustaining burns from one of the vaporizers which was not being watched carefully during use. It might be

worth calling attention to the vaporizer which has a nozzle 2 to 3 feet long. It contains a large volume of water. It continues to operate for six to eight hours if necessary and it is not very expensive. It costs about $10, but it is worth it when one considers that it eliminates the hazard of the other vaporizers which have to be placed dangerously close to the child's bed. When it is in use, the crib is covered with a sheet like a covered wagon, the steam entering through an opening at the foot and leaving through an opening near the baby's face. There is no danger of splashing. The way we commonly use it is to have it operate for twenty minutes at intervals of approximately four hours. We find the steam inhalation extremely useful in cases of laryngeal spasm, the croupy kind of cough which is much more frequent among children than among adults. The croupy cough which sounds like the bark of a seal is frightening. Inhaling warm steam relaxes the laryngeal spasm fairly quickly. Syrup of ipecac is also quite effective in promptly terminating the croup but there is the fact that the doses used provoke vomiting.

We have a great deal of respect for croup. If it lasts unduly long, we are apt to treat the child with penicillin or even streptomycin. Some of the cases develop into laryngotracheobronchitis, a very serious infection which rapidly extends down the respiratory tree, producing an undue amount of edema, and may prove rapidly fatal in between 25 and 50 per cent of the cases. If, in a case of croup the child's distress persists, the temperature continues to rise and weakness seems unduly pronounced, penicillin and streptomycin should be used promptly and the steam inhalation.

A foreign body in the respiratory tree is not a very rare cause of coughs in children. In the process of swallowing the various and sundry items they put in their mouths, they also inhale. One therefore finds peanuts, toys, marbles and pennies which require removal. It is a good plan to examine the child behind the fluoroscopic screen. The mediastinum is likely to move in the direction of the bronchus containing the foreign body. If one informs the bronchoscopist of this fact, he can go right ahead with the business of removing the foreign body. Some of the inhaled foreign bodies give rise to a rapid inflammatory process; in the case of a peanut there may be extreme inflammation in the area within six to twelve hours after the article is inhaled. By the way attention should be called to the fact that turning the child upside down and pounding the back for the purpose of recovering a foreign body is a dangerous procedure, because often the result is not the one expected; the article is not recovered but thrown into one of the upper bronchi, from which removal is more difficult.

I have referred to the need for making medicines pleasant for children. In the case of pharyngitis we sometimes give them hard candy, honey and pieces of ice to suck on. All of these occasionally prove helpful. In the cough of more chronic conditions such as adenoiditis, spray with penicillin takes care of the condition. In some cases the condition is resistant until the adenoids are removed.

Bronchitis in children is managed in much the same way as it is in adults, namely, with antibiotics and postural drainage.

Lipoid irritations occur much more frequently in children than in adults because of the common use of oily nose drops in the several preparations of commerce. They are not used as frequently now as they used to be. Another source of inhalation of oil has also greatly diminished. In the old days it was the practice to take advantage of the baby's screaming and while the mouth was wide open, the teaspoonful of cod liver oil was popped in. The operator was not certain whether the material was swallowed or inhaled but further experience showed that a good deal of it was inhaled, with the result that an interstitial inflammatory reaction was set up in the lungs. In present days we are much more conscious of the lipoid irritations from nose drops; when they appear, the drops are discontinued and the cough subsides.

Pediatricians have shown interest in the use of atropine or belladonna in the cough problems of children but I believe it is of no particular value unless there is an unusual amount of bubbling. It should never be used in laryngitis or laryngospasm of the child. The dose is very small, $\frac{1}{1000}$ gr. or 0.06 mg.

Whooping cough is one of our problems. We obtain some aid from codeine in a dose of 15 mg. every four hours, increasing the dose until the level is high enough to give rise to perceptible benefits. I might mention parenthetically that chloromycetin has received a trial in whooping cough recently. I have not had much experience with it but there are pediatricians who have made very optimistic reports on its use in doses of 100 mg. per kg., essentially the same dosage

as that for aureomycin in the treatment of whooping cough.

We treat the cough of asthma in children in much the same way as in adults. If the child is old enough, we employ epinephrine 1:100 in the nebulizer. A child over three years of age can be taught how to use it. The mixture of aminophylline and phenobarbital is given by mouth or by suppository. We are inclined to avoid the intravenous injections in children.

I might say a word about narcotics in the treatment of coughs of children. I have referred to the use of codeine. I should mention that I often use dionine instead of codeine. It is my impression that it is less constipating. I have not used dilaudid in children, although it may well be that other pediatricians do use it. The customary dose of dionin is $\frac{1}{32}$ gr., or approximately 2 mg.

DR. MUSCHENHEIM: I see that Dr. Gold has been making copious notes. Maybe he would let us in on some of his reflections.

DR. CATTELL: Dr. Gold, would you wish to enlarge on some of your earlier remarks, or have you additional remarks concerning cough medicines since you have heard the various discussions?

DR. GOLD: The treatment of cough seemed to be a fairly simple problem at first, but as I listened to the various discussions and reflected on them the subject seemed to grow in complexity. The questions that come up are numerous. Cough is commonly looked upon as an involuntary reflex performance. It is undoubtedly that in a great many situations but it takes little effort to realize that cough may be a purely voluntary physiologic act. There is the chain smoker who develops a troublesome cough. He arises in the morning and as he takes a few breaths he becomes aware of mucous moving up and down in the trachea. He promptly starts to cough for the purpose of dislodging it. This is a purely voluntary act. As he goes on with it, however, the cough may be changed from a voluntary performance to an involuntary reflex due to stimulation from the plaques of mucus which he was unsuccessful in dislodging completely. He ceases smoking for a period of days or weeks and the cough vanishes. Little is gained by the use of cough remedies in such cases.

There are the patients with minor irritation of the upper respiratory passages which gives rise to a mild cough and perhaps colorless expectoration. In the course of time a secondary infection changes the character and quantity of the mucus, and with these there is an increase in the intensity of the morning period of coughing. In such cases the cessation of smoking and a few doses of penicillin promptly bring the mucus back to the colorless state and also bring the severe morning cough under fairly complete control. So far no cough medicines have been used.

Reference has been made to the patient with allergic asthma. He is free of cough until he finds himself exposed to the particular allergen, such as dust or dander. He begins to wheeze and cough. This type of cough is often persistent, non-productive and exhausting. A small dose of epinephrine, perhaps no more than 0.25 cc. of a 1:1000 solution given subcutaneously, eliminates the wheeze and brings the cough under control within a matter of minutes. In these, the mechanism of the cough is probably excitation of the sensory fibers in the respiratory passages by swelling of the mucous membrane, and the control of the cough is not brought about by a specific cough remedy but by a drug which causes vasoconstriction with shrinking of the mucous membranes.

Another special variety is that of the patient with a disorder of cardiac rhythm, especially frequent premature contractions. This is an annoying type of cough problem in which the respiratory passages do not seem to be involved directly at all. Every time the heart discharges an extra beat the patient coughs, probably as the result of a reflex arising from the heart or great vessels. Most patients pay little or no attention to it but there are some in whom the cough caused in this way may prove very disquieting.

The case of cough resulting from congestive heart failure is of particular interest. It is well to emphasize this variety for it is frequently overlooked, and patients are treated for long periods of time with various cough remedies without avail. The misleading trick here is the fact that cough may be the patient's only presenting symptom. On careful questioning one may elicit an equivocal history of shortness of breath on exertion but a large proportion of these patients are free of physical signs of congestive failure; no pulmonary rales, no enlargement of the heart, no enlargement of the liver and no edema of the extremities. One's attention is sometimes focused on this group by the

fact that the cough is most troublesome when the patient lies down at night and is relieved by propping the head with extra pillows. But these matters come to light only if the physician has the problem in mind and asks the proper questions. The common cough remedies are of little or no value in these cases but the response is dramatic when the patient is digitalized or placed on a system involving a low salt diet and two or three injections of a mercurial diuretic per week, or as frequently as is necessary.

Then there are the patients with primary cardiac disease and advanced mitral stenosis. In these the pulmonary vascular pressure often rises considerably. Pulmonary congestion is the dominant state. The congestion may be so pronounced that not only is cough brought on but also the cough may be associated with bloody expectoration. Slight infection superimposed on this type of pulmonary state often results in diffuse pulmonary rales and signs suggesting acute bronchitis or pneumonia. These patients often present a history of having had numerous attacks of pneumonia, these attacks having been, in fact, not pneumonia at all but the result of superimposed minor respiratory infection on a pulmonary membrane in which the capillaries were already highly distended. A few days of complete rest with elevation of the head to reduce pulmonary vascular pressure often suffices, in this group, to bring to an end a most troublesome type of cough with bloody expectoration. The results are greatly aided by digitalization, mercurial diuretics and salt-restricted diet.

I am not certain that it is a fact but I have the impression that, at least as often and perhaps more often than not, the control of cough lies in measures other than specific cough remedies.

DR. CATTELL: Dr. Lansdown, I would like to ask a question concerning your choice of preparations. I notice that you have listed ephedrine, epinephrine and vaponefrin. Why all of them?

DR. LANSDOWN: I have been using ephedrine in sinusitis because huge quantities are needed and the drug is not very costly. I prescribe vaponefrin for patients with marked bronchiolar spasm and emphysema for use as an inhalant. The patient takes it himself and is not dependent on the doctor for an injection.

DR. CATTELL: I think we should draw attention to the fact that vaponefrin is simply epinephrine marketed with an atomizer for oral inhalation. Vaponefrin was advertised with claims of superiority. The Council on Pharmacy and Chemistry investigated the matter and reported on it in the *Journal of the American Medical Association* on September 26, 1942. It turned out that vaponefrin is an approximately 1:40 solution of racemic epinephrine provided for inhalation. It is therefore just a little more potent than the 1:100 NNR epinephrine solution for use by inhalation, because U.S.P. epinephrine is levorotatory and the racemic form represents equal parts of levo- and dextrorotatory compounds, the dextrorotatory compound being only about $\frac{1}{15}$ as potent as the levocompound.

DR. WALTER MODELL: Does the epinephrine inhalant or vaponefrin produce its effect by a local action or after absorption?

DR. CATTELL: There is some controversy about that point. It is said that the action is local. I would like to see some satisfactory proof.

SUMMARY

DR. GOLD: I think that one of the most useful aspects of the discussion today on the treatment of cough is the perspective that was developed in relation to this problem. The fact that a patient has a cough does not indicate that he is in need of treatment for it. Some coughs are a kind of nuisance which the patient might be allowed to bear without treatment. There are conditions in which the need is not to stop a cough but to produce one. That cough is not always an involuntary reflex activity, but often a voluntary action controlled by the patient, is a view which is not commonly formulated in writings on the subject.

That treatment of cough is more than the choice of a cough remedy is a fruitful approach to the problem. Questions that need to be dealt with before treatment were brought to our attention: Is the origin of the cough a sinusitis, tracheitis, bronchitis, infection in the pulmonary alveoli, a dry pleurisy, or some disorder outside of the lungs; is the origin an infection or a tumor or enlarged lymph nodes?

Some of the essential measures in the management of cough were enumerated and described, namely, constant temperature in the patient's atmosphere, warmth, the ice collar and the vaporizer. We received some instruction in the technic of applying vaporizers, points regarding their dangers and a view on the utility of medicated vapors. The place of postural drain-

age and the technic were elaborated. In chronic coughs emphasis was placed on the need of educating the patient to make the best use of the cough, to avoid unnecessary troubles from noisy blasts and emptying the lungs of material at the appropriate time so as to curtail the degree to which the cough interferes with the patient's social life and rest at night.

Only a few medications for the treatment of cough were mentioned and attention was called to the fact that much disagreement exists in the choice of cough remedies. It seems to be a field in which polypharmacy and shotgun mixtures have enjoyed immunity from attack, for it makes very little difference what the ingredients are or how many are included if the mixture only expresses the art of mixing palatable materials. However, the cough remedy, if seriously considered, is more than a palatable or unpalatable vehicle. The principle was elaborated that, aside from the flavoring materials, the cough mixture which is taken by mouth contains one or another irritant, nauseant or emetic which by a reflex action causes a change in the respiratory secretions. In patients with cough these may be either too abundant, too scant, too thick or too tenacious. The suggestion was made that the term "expectorant" be confined to these peripherally acting materials. In addition, there is the opiate, the action of which is central to depress the cough mechanism in the central nervous system. All potent cough remedies, therefore, contain an opiate and an expectorant, and these two are put into an appropriate vehicle. There are different expectorants such as terpin hydrate, antimony and potassium tartrate, ipecac and others. There are also different opiates such as codeine, dionin, morphine and others. We were left without a precise answer to the question of choice. Is there evidence that any particular expectorant or opiate in a cough mixture is more effective than any other for all coughs or any particular kind of cough? The choice seems to be based upon use and familiarity.

In addition to the foregoing matters the conference explored other items of interest in connection with cough, such as the mode of action of iodides, the special problems of treating cough in children, the surgical approach to some kinds of cough, the wide variety of conditions producing cough and requiring medical treatment but not the specific cough remedy and the place of bed rest in the management of cough.

Clinico-pathologic Conference

Hepatomegaly, Ascites and Hepatic Failure

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, C. W. (No. 212996), was a farmer and merchant, fifty-seven years of age, who was admitted to the Barnes Hospital for the first time on August 12, 1952, complaining of anorexia, weakness and abdominal distention. The family history was of interest in that the patient's father had died at the age of forty-nine of heart disease, one brother had died of "a heart attack" and another brother was said to be suffering from heart disease. The patient himself had enjoyed generally good health. Although he had consumed a moderate amount of alcohol for a period of years, his diet had always been adequate. In the two-year period prior to the onset of the present illness, the patient stated that his health had deteriorated somewhat. During this period he had had an appendectomy from which he recovered uneventfully, but he did not recall any other specific complaints.

Seven years before admission he suddenly developed a severe, aching, constant pain in the left flank, associated with anorexia and weakness but not with urinary symptoms. He could give no other information about the illness. He was admitted to an outside hospital where splenectomy was performed, and for one year thereafter he received frequent blood transfusions. During this period his health gradually improved and he was able to return to work. During the following three years he did quite well. He then developed sudden epigastric pain which his physician considered to be cardiac in origin, and he was kept in bed for one month and given digitalis. A chest film taken at this time was said to have shown the heart to be normal in size. The patient was told that the film showed that he had inactive fibrous pulmonary tuberculosis.

In the next two years he indulged in mild physical activity. During this period he had one episode of massive hematemesis for which he received blood transfusions. He was told that he had a gastric ulcer and an ulcer diet was prescribed. One year before entry the patient experienced several attacks of severe precordial pain and eventually developed the signs of myocardial infarction. Following recovery from the acute episode, he remained physically incapacitated, his appetite diminished and in the course of the year he lost about 40 pounds. A month before his admission to the Barnes Hospital, he developed progressive weakness and fatigue. His urine became dark in color, his stools light and progressive abdominal distention developed. The patient denied jaundice during the month prior to entry. On the day before admission a paracentesis was done with removal of ascitic fluid, and the patient was then referred to the Barnes Hospital.

Physical examination at the time of entry revealed his temperature to be 36.5°C., pulse 86, respirations 22 and blood pressure 118/90. The patient was a well developed but poorly nourished man who appeared chronically ill. The skin and sclerae revealed a moderate degree of icterus and there were scattered small ecchymotic areas over the body, particularly at the site of hypodermic injections. The pupils reacted normally to light and accommodation. The fundi showed only moderate arteriosclerotic changes. Dried blood was noted in the left nostril. Examination of the upper respiratory tract was otherwise not remarkable. There was no generalized lymph node enlargement. Examination of the lungs revealed bilateral dullness to percussion and diminished breath sounds below the sixth rib anteriorly, and laterally and posteriorly at the same level. Fine and medium coarse rales were heard over the remainder of the lung fields. The heart was essentially normal to examination. The abdomen was protuberant, and there was a draining paracentesis wound just below the umbilicus. The abdominal veins were distended with blood flow being cephalad. A fluid wave and shifting dullness were easily

demonstrable. The liver edge was palpable 5 cm. below the costal margin and was firm and somewhat tender. No other organs or masses were felt. The left testis was atrophic. Moderate presacral, scrotal and ankle edema were present. The neurologic examination was within normal limits.

The laboratory data were as follows: Blood counts: red cells, 5.11 million; hemoglobin, 13.9 gm.; white cells, 24,000; differential count: basophils 1 per cent, eosinophils 5 per cent, stab forms 2 per cent, segmented forms 78 per cent, lymphocytes 10 per cent, monocytes 4 per cent. There was moderate anisocytosis of the red blood cells. Platelet count, 63,450. Clotting time: 7 minutes. Bleeding time: 4 minutes. Urinalysis: specific gravity, 1.017; reaction, 5.0: albumin, 1+; sugar, negative; microscopic, negative; urobilinogen, negative; bilirubin, positive. Stool guaiac, trace. Cardiolipin test: negative. Sputum: negative for acid-fast bacilli. Blood chemistry: non-protein nitrogen, 33 mg. per cent; sodium, 134.5 mEq./L; potassium, 4.4 mEq./L; chloride, 101 mEq./L; CO_2 combining power, 25.7 mEq./L; total proteins, 6.9 gm. per cent; albumin, 2.3 gm. per cent; globulin, 4.6 gm. per cent; sodium bilirubinate, 2.66 mg. per cent; bilirubinglobin, 4.84 mg. per cent; total bilirubin, 7.5 mg. per cent; alkaline phosphatase, 9 Bodansky units; prothrombin time, 31 per cent of normal; cephalin-cholesterol flocculation test, 3+; zinc flocculation test, 3+; thymol turbidity, 2.1 units. Electrocardiogram: findings consistent with old posterior myocardial infarction.

The patient's hospital course was one of progressive deterioration. He was given a high protein, high calorie diet but his oral intake was unsatisfactory and parenteral feedings were necessitated. Despite massive doses of vitamin K intravenously, there was no change in the prothrombin time. Because of the patient's critical condition, neither a liver biopsy nor x-ray studies, both of which were planned, could be performed. The patient bled massively from the gastrointestinal tract and required multiple transfusions. The non-protein nitrogen rose to 50 mg. per cent; and although large amounts of parenteral fluids were given, the sodium fell to 129.5 mEq./L. and the potassium rose to 6.2 mEq./L. Jaundice progressively deepened. The patient complained of upper abdominal pain and became increasingly restless and mentally confused. Shortly before death he again vomited large amounts of bright red blood. His blood pressure became unobtainable, he lapsed into deep coma and expired quietly on August 19, 1952.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This patient evidently had several diseases, including cirrhosis of the liver, coronary atherosclerosis and myocardial infarction and possibly pulmonary tuberculosis in an inactive stage. Since his liver disease probably was responsible for his death, it will be profitable to consider this aspect of the case in detail. The history suggests that the patient's health first became impaired about ten years before entry, although he was unable to describe any specific symptoms which he had during this period. Seven years before entry, however, he suffered an attack of left-sided abdominal pain. He was subjected to splenectomy, and subsequently received multiple transfusions during the ensuing one-year period. Unfortunately, we lack information concerning the indications for splenectomy. It is of interest, however, that for a three-year period, beginning one year after splenectomy, the patient apparently enjoyed good health. Then he developed evidence of progressive coronary artery disease and he had one episode of hematemesis. In the year before entry his health failed seriously, and by the time he entered the Barnes Hospital he was in critical condition. Dr. Moore, would you begin the discussion by considering the indications for splenectomy in patients with cirrhosis.

DR. CARL V. MOORE: In the presence of congestive splenomegaly or secondary hypersplenism one is justified in recommending splenectomy in cirrhotic patients. Hypersplenism can manifest itself either by hemolytic anemia, thrombocytopenic purpura or more rarely by granulocytopenia. Insofar as the case under discussion is concerned it is impossible to tell why the spleen was removed, although the patient presumably had anemia, perhaps due to Banti's syndrome. It seems likely that he continued to bleed after splenectomy for he was given transfusions frequently in the following year. Then apparently the bleeding ceased and the patient did well for three years. It is also possible that originally the patient had a hemolytic anemia which did not respond to splenectomy, thus necessitating the transfusions. If the

hemolytic anemia were related to the liver disease, it would have to be termed a symptomatic hemolytic anemia. On the other hand, acquired hemolytic anemia, unrelated to the liver disease, may have been present. If so, splenectomy was ineffective. An interesting feature of this case is that prior to splenectomy, the patient had left upper quadrant pain. When such pain is associated with splenomegaly, it is usually due to an extremely large spleen or to an infarct or perisplenitis. It is not possible to differentiate between these on the basis of the information at hand.

DR. ALEXANDER: The term Banti's syndrome is frequently confusing. Would you clarify it for us.

DR. MOORE: There is no uniform agreement as to what name one should use for the syndrome of congestive splenomegaly and hemolytic anemia or thrombocytopenia. The term hypersplenism has also been used. I see no objection to the use of "Banti's syndrome" as long as it is recognized that in Banti's syndrome the splenic abnormality is congestive in nature and is secondary to the lesion producing splenomegaly.

DR. ALEXANDER: If the spleen is removed in so-called Banti's syndrome, is the treatment usually successful? As you have pointed out, this patient did quite well for a number of years after operation.

DR. MOORE: It is believed by some clinicians that splenectomy may result in improvement as far as hemolytic anemia or thrombocytopenia is concerned, but bleeding from esophageal varices remains a serious hazard. There is one point in the history, Dr. Alexander, which suggests that this patient may not have had congestive splenomegaly but rather idiopathic acquired hemolytic anemia. Because of the lack of adequate data one can only speculate at best, but it should be remembered that the patient's platelet count was 63,000 at the time of his admission to this hospital. If he had had congestive splenomegaly causing hemolytic anemia, there would be no adequate explanation for the thrombocytopenia which developed subsequently to splenectomy. On the other hand, if he originally had idiopathic acquired hemolytic anemia, it is clear from the work of Evans and others[1] that thrombocytopenia is frequently associated with idiopathic acquired hemolytic anemia, not necessarily concomitantly. Thus an individual may have hemolytic anemia at one time and thrombocytopenic purpura at another.

DR. ALEXANDER: It seems clear that when the patient entered the hospital, he exhibited the signs of hepatic failure. Dr. Shank, the statement is made that the patient drank a moderate amount of alcohol for a period of years but took an adequate diet. Would you discuss the current concepts regarding diet and alcohol in the etiology of cirrhosis?

DR. ROBERT E. SHANK: A history of excessive intake of alcoholic beverages has been obtained in about 50 to 70 per cent of the cases of portal cirrhosis studied in various clinics throughout the United States. Frequently, in association with excessive alcoholic intake, patients take inadequate diets, particularly in regard to protein and other protective nutrients. It should be emphasized, however, that there are parts of the world where cirrhosis is common and alcoholism uncommon. For example, cirrhosis is one of the chief causes of death among Hindus, yet this group of people does not drink alcohol because of their religious beliefs. Their diets, however, are low in protein and in some of the water-soluble vitamins. Similarly, among certain natives in the southern part of Africa cirrhosis of the liver is common, although the intake of alcohol is much lower than in the United States. I think that the available evidence indicates that an inadequate diet is of prime importance in the development of cirrhosis. Whether or not alcohol functions as a toxin *per se* is still a matter of question in my opinion, but there are those who hold to this view. Certainly it merits further consideration.

DR. ALEXANDER: Does a significant number of patients with hepatitis eventually develop portal cirrhosis?

DR. SHANK: Certainly some do. The experience is variable. In some clinics as many as 10 to 20 per cent of the patients who die of portal cirrhosis have histories of previous viral epidemic hepatitis. I do not believe, however, that the importance of viral hepatitis in development of portal cirrhosis can be definitively evaluated yet.

DR. ALEXANDER: In view of your concepts about the etiology of cirrhosis, would you summarize the measures which you consider most important insofar as treatment is concerned.

DR. SHANK: One of the major problems which the physician faces in treating patients with cirrhosis is to get them to eat an adequate diet—

[1] EVANS, R. S., TAKAHASHI, K., DUANE, R. T., PAYNE, R. and LIU, C. Primary thrombocytopenic purpura and acquired hemolytic anemia. *Arch. Int. Med.*, 87: 48, 1951.

one containing sufficient protein and adequate amounts of water-soluble vitamins. It is of interest in this regard to consider the case under discussion. This patient, like many others with cirrhosis, gave a history of rather prolonged anorexia, and thus of poor dietary intake, prior to the development of hepatic failure. It may be most difficult, and sometimes impossible, to get these patients to eat adequately. In addition to a proper diet it has been recommended that lipotropic substances be given—choline, inositol and methionine. It is questionable if these substances are needed by those patients who eat a sufficient diet. On the other hand, they may have a place in the treatment of acute fatty infiltration of the liver.

DR. ALEXANDER: Would you comment on the use of crude liver extract in the treatment of cirrhosis?

DR. SHANK: During World War II, in studies carried on at the Rockefeller Institute, we gave large doses of crude liver extract intramuscularly to patients with cirrhosis, and were impressed by the therapeutic response. Because the dose which could be given by the intramuscular route was limited, we prepared an extract for intravenous use which we gave in amounts up to 150 cc. weekly. It was our belief that the patients who received the extract intravenously did well. We were unable to characterize the effective principle or principles in the preparation. We were impressed by the fact that in patients who were anoretic and had eaten poorly the intravenous extract appeared to enhance the appetite and the dietary intake. At present there is only one crude liver extract of comparable type available, and it unfortunately often causes vasomotor collapse. For this reason we do not employ it. The fact remains that if one can induce patients with cirrhosis to increase their diet to adequate amounts, one may help them to improve significantly.

DR. ALEXANDER: Dr. Mendeloff, would you comment on the liver function tests which were done on this patient? These studies were limited by the patient's downhill course.

DR. ALBERT I. MENDELOFF: In general, the results of the liver function tests were similar to those often found in patients with chronic liver disease. Abnormal cephalin-cholesterol flocculation tests are common in cirrhotic patients with jaundice, but the test is often negative when the liver is reasonably well compensated. Zinc flocculation is a specific measure of gamma globulin increase; the 3+ result in this case is compatible with the hyperglobulinemia recorded. An abnormal zinc flocculation test, coupled with reversal of the albumin-globulin ratio, is typical of parenchymatous liver disease. The normal thymol turbidity test is not an unusual finding in chronic liver disease, and may be related to the relatively low serum lipid which some patients with advanced cirrhosis exhibit. Slight elevation of the alkaline phosphatase is a common finding in both acute and chronic forms of liver disease. A prothrombin time 31 per cent of normal is also in the range found in serious chronic liver disease, and of course is the result of the inability of the liver to synthesize prothrombin. When hypoprothrombinemia is due to hepatocellular damage, massive doses of vitamin K parenterally are almost always without avail.

DR. ALEXANDER: Would you comment on the fractional bromsulphalein clearance test[2] in which you are interested?

DR. MENDELOFF: The test is not specific, but indicates the per cent of total plasma volume cleared of the dye per unit time. This value is uniformly reduced to levels of 3 to 6 per cent per minute in patients with portal hypertension complicating chronic liver disease. The test is sensitive and may be the only clue to the existence of severe liver disease when many other so-called liver function tests are normal.

DR. ALEXANDER: It is said that liver function does not become critically impaired unless 80 per cent of the liver is destroyed. Since this patient died in liver failure, Dr. Scheff, one may reasonably assume that his liver was for the most part destroyed. It would seem somewhat unusual, therefore, that it was so large. Would you comment on this point, Dr. Scheff?

DR. HAROLD SCHEFF: Because regeneration of hepatic cells is a common feature of serious liver disease, the liver may be quite large in advanced cirrhosis although, as you suggest, late in the disease it usually is not. The size of the liver in this case may indicate the presence of another lesion, i.e., a tumor.

DR. ALEXANDER: Do you believe that regenerative cells function? In other words, is it possible for a patient to die of liver failure when the liver is the site of active regeneration?

[2] INGELFINGER, F. J., BRADLEY, S. E., MENDELOFF, A. I. and KRAMER, P. Studies with bromsulfalein. I. Its disappearance from the blood after a single intravenous injection. *Gastroenterology*, 11: 646, 1948.

DR. SCHEFF: Liver failure certainly occurs in the presence of regeneration.

DR. SHANK: I would like to agree with Dr. Scheff. Considerable regeneration of hepatic tissue is frequently noted in the microscopic sections of livers from patients who have died in hepatic coma.

DR. ALEXANDER: Then we will accept the possibility that the patient's liver may have been large because of active regeneration. Dr. Scheff, you remarked that the liver could have been the site of a tumor. Would you enlarge on this suggestion?

DR. SCHEFF: Patients with cirrhosis of the liver are more apt to develop hepatomas than are normal individuals, and in view of the degree of hepatomegaly, the diagnosis of hepatoma should be considered.

DR. ALEXANDER: Do you think fatty infiltration is a likely explanation of the large liver?

DR. SCHEFF: Although fatty infiltration can produce hepatic enlargement, it is a feature of early rather than of late cirrhosis. I don't believe it is likely in this case.

DR. ALEXANDER: May we now turn to the cardiovascular problem. Dr. Smith, this patient gave a history compatible with myocardial infarction. He presumably had marked physical limitation because of coronary artery disease, and when he was admitted the findings included bilateral pleural effusion, pulmonary congestion as evidenced by the presence of many moist rales, edema and ascites. His heart was normal in size and the blood pressure was not elevated. Dr. Owen, who was taking care of the patient, told me that an x-ray of the chest, taken three weeks before the patient was admitted to the Barnes Hospital, confirmed the fact that the patient's heart was normal in size. An electrocardiogram showed the changes of an old infarction. On the other hand, as I went through the record carefully, I found no mention that the patient had ever experienced dyspnea or orthopnea, and it was specifically stated that his neck veins were not distended. Considering all of these observations, do you think the patient was suffering from cardiac failure?

DR. JAMES OWEN: I would like to add one other bit of information, Dr. Alexander, namely, that the patient's circulation time with decholin was 16 seconds.

DR. JOHN R. SMITH: Certainly some of the clinical features—ascites, edema, pleural effusion and pulmonary congestion—are suggestive of heart failure. On the other hand, when congestive heart failure proceeds to such an extent that the aforementioned signs are noted, usually the venous pressure is distinctly elevated, cyanosis is commonly present, cardiac enlargement is noted and one expects the patient to complain of dyspnea. The diagnosis of coronary artery disease cannot be questioned, and the myocardium was probably seriously compromised as a result. Nonetheless, I would find it difficult to make an unequivocal diagnosis of congestive heart failure because of the reasons I have mentioned.

DR. ALEXANDER: If it is assumed that the patient did not have congestive heart failure, Dr. Goldman, can you explain the bilateral pleural effusion and rales on the basis of pulmonary disease? The patient was once told that he had inactive tuberculosis.

DR. ALFRED GOLDMAN: No, I can't. Despite the reported x-ray changes of inactive tuberculosis, there is little in the history or in the course of the patient's illness to suggest that tuberculosis played any part, and there is nothing to suggest any other pulmonary disease.

DR. ALEXANDER: Dr. Karl, is edema of the lower extremities common in the presence of ascites and portal cirrhosis?

DR. MICHAEL M. KARL: Yes, it is and usually arises on the basis of several factors. First, the serum albumin is so low that the osmotic pressure of the blood is significantly decreased. Second, the presence of ascites may compress the vena cava to a considerable extent and favor the development of edema.

DR. ALEXANDER: Would you comment on the evidence that hormonal influences may also be active.

DR. KARL: There are data which suggest that in cirrhosis an excess of pituitary antidiuretic factor influences the retention of fluid. Sodium retention has not only been demonstrated by the finding of decreased sodium in the urine but also in tears and sweat. All of these factors may be operative in a given case.

DR. ALEXANDER: What form of treatment is preferable in your opinion for patients with severe liver disease and ascites?

DR. KARL: First of all, I would like to add to Dr. Shank's comments on the use of crude liver extract. There is evidence to suggest that the administration of crude liver may enhance the excretion of antidiuretic factor. Further,

there are those who believe that crude liver extract contains growth factors which are of value in hepatic regeneration. Liver is probably a good source of lipotropic substances, perhaps more so than choline, methionine or other preparations. Dr. Ralli[3] has shown in a careful study that the administration of crude liver is probably more effective than any other single therapeutic measure in reducing ascites. Indeed, her data suggest that crude liver is even more valuable than a low sodium diet. Other measures which may be employed include the use of mercurial diuretics and paracenteses. The latter procedure has its disadvantage in that the protein content of ascitic fluid is high, and the frequent removal of ascitic fluid constitutes an added drain on protein. Although protein is probably of little value while in ascitic fluid, if the fluid can be resorbed, the protein therein becomes useful again. Finally, general supportive measures such as bed rest may be beneficial.

DR. ALEXANDER: On the basis of what has been said, we can perhaps account for many of the findings which suggest cardiac failure on the basis of the liver disease, but we still have not explained the bilateral hydrothorax and the presence of rales. Dr. Bukantz, do you have any suggestions about this aspect of the problem?

DR. SAMUEL C. BUKANTZ: It is conceivable that the pleural effusions arose on the same basis as the ascites and edema, primarily hypoalbuminemia and sodium retention.

DR. ALEXANDER: It seems to be the consensus that the patient probably did not have congestive failure, and that the fluid retention was due to liver disease. Dr. Scheff, you suggested that a hepatoma, developing in a cirrhotic liver, could have explained the very large liver. Do you think it is likely that the tumor had metastasized to the pleurae? If so, the pleural effusion could be explained on that basis.

DR. SCHEFF: Yes, hepatomas metastasize widely, and commonly to the chest.

DR. ALEXANDER: I had occasion to look up statistics bearing on this point and found that in one large series 20 per cent of the patients with hepatomas had metastases to the pleurae.

DR. BUKANTZ: In view of the fact that the patient is said to have had a gastric ulcer, the possibility of carcinoma of the stomach with hepatic and pleural metastases is worth mentioning.

DR. KARL: When I saw this patient in consultation with Dr. Owen, the explanation of the large, hard liver was not clear. The findings did not suggest that fatty infiltration was responsible for the size of the liver. As mentioned earlier, considerable regeneration of hepatic tissue could have resulted in a large, hard liver. But if one assumes that the thymol turbidity test is an index of regenerating liver, the normal result of the test in this case is against much regeneration. Further, the combination of a very large liver and rapidly reaccumulating ascitic fluid is not common in terminal liver failure. Rather the liver is apt to be normal in size or even small. Since neither fatty infiltration or regeneration of the liver was compatible with the clinical picture, primary or secondary carcinoma was considered. Hepatoma seemed more likely because of the high incidence of hepatoma in cirrhosis. Metastatic tumor to the liver would have necessitated relegating cirrhosis to the category of an "incidental finding." In any case, there could be no doubt that the patient had cirrhosis of advanced degree.

DR. BUKANTZ: Do the liver function studies enable one to differentiate diffuse parenchymal involvement from carcinomatous infiltration?

DR. MENDELOFF: Usually when there is extensive carcinoma in the liver without underlying parenchymal disease, the alkaline phosphatase tends to be high but the bilirubin is usually not elevated significantly. This pattern is not always observed under such circumstances but it is common. As has been mentioned, the results of the various tests in this case were typical of cirrhosis. A somewhat unusual feature of the case was the fact that the patient was fifty years old when he apparently had congestive splenomegaly as the first sign of the disease.

DR. FREDERICK G. GERMUTH: I would like to clarify the statistics relating hepatomas to cirrhosis. Approximately 5 per cent of patients with cirrhosis develop hepatomas. On the other hand, if one considers the question from the point of view of hepatomas, it is found that 70 per cent of these tumors arise in cirrhotic livers.

DR. ALEXANDER: We are in agreement, I think, that cirrhosis of the liver, probably with a hepatoma, is the most likely diagnosis with

[3] RALLI, E. P., LESLIE, S. H., STUECK, G. H., JR., SHORR, H. E, ROBSON, J. S., CLARKE, D. H. and LACEN, B. The course of cirrhosis of the liver in patients treated with large doses of liver extract intravenously. *Medicine*, 28: 301, 1949.

metastatic carcinoma of the liver, originating in the stomach, as an unlikely second choice.

Clinical Diagnoses: Cirrhosis of the liver; hepatoma with metastases to the pleurae; ? carcinoma of the stomach with metastases to the liver and pleurae.

in the left lobe and was surrounded by small satellite nodules. It invaded the portal vein, which was occluded by thrombus and tumor. The tumor also grew into the hepatic veins and into the inferior vena cava, as is shown in the section of the pancreas and vena cava in the

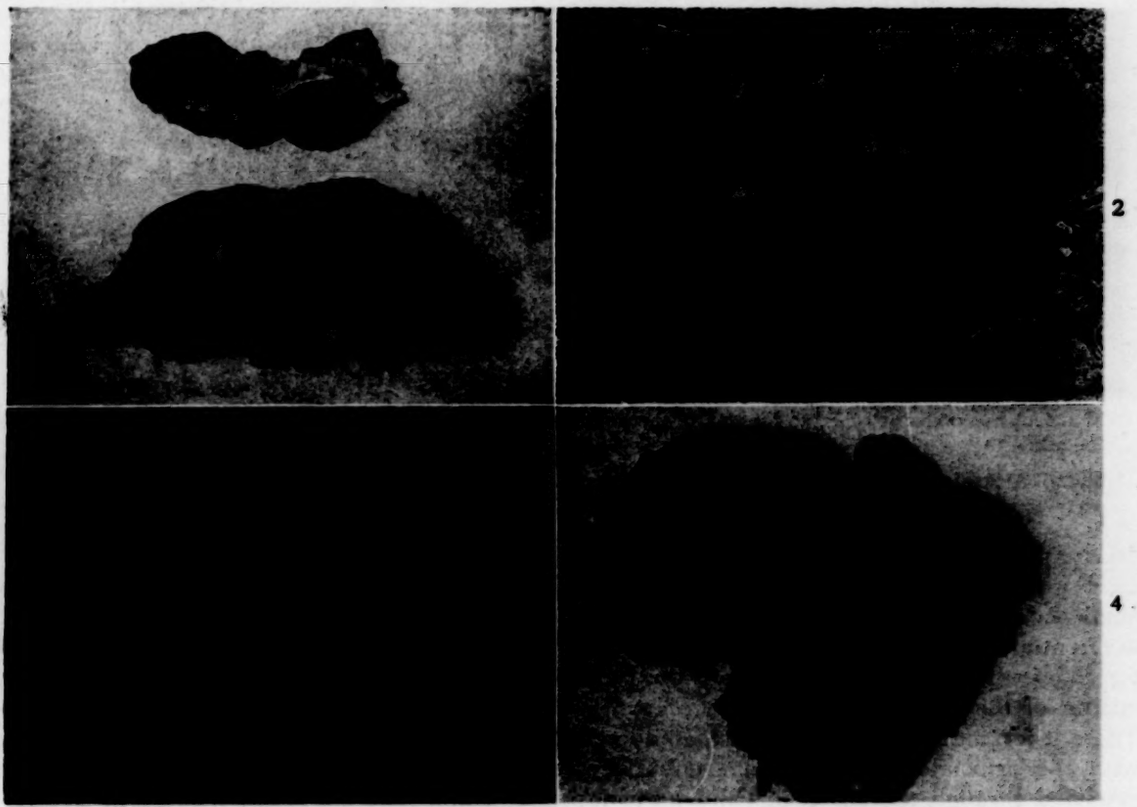

FIG. 1. Below, a section through the liver showing diffuse nodular cirrhosis and a large nodule of variegated tumor in the left lobe; above, the inferior vena cava as it passes through the pancreas is invaded and filled by tumor.

FIG. 2. Cirrhosis of the liver with a well delineated nodular pattern; many lymphocytes in the stroma suggested some activity of this process.

FIG. 3. Hepatoma with markedly pleomorphic and anaplastic cells.

FIG. 4. The heart showing a thrombus of tumor and clotted blood that entered through the inferior vena cava, filled most of the right atrium and extended through the tricuspid valve into the right ventricle. The heart is viewed from the rear with the septum and left ventricle raised upward.

PATHOLOGIC DISCUSSION

DR. FREDERICK G. GERMUTH: Fresh blood was present in the oral cavity and nose at the time of autopsy and the tissues were moderately icteric. Gross examination of the liver showed diffuse nodular cirrhosis, as illustrated in Figure 1. The liver was composed of small nodules of hypertrophic hepatic tissue between septa of dense grey fibrous tissue. Superimposed upon the cirrhosis was a large nodule of white, firm tumor in which there were foci of hemorrhage and yellow necrosis. The main tumor was

upper portion of Figure 1. The episode of ascites and edema of the legs which developed late in this patient's history were probably related to the establishment of complete obstruction by these tumor thrombi. Figure 2 shows a microscopic section of a common type of cirrhosis with sharply outlined nodules. The presence of a fair number of lymphocytes in the fibrous tissue about the hypertrophic nodules suggested some activity despite the sharp delimitation of the nodules themselves. There was no necrosis in this liver and remarkably little

congestion when one considers the obstruction of the hepatic vein.

Sections of the tumor (Fig. 3) presented a bizarre, anaplastic picture with pleomorphic cells of various sizes and nuclear configuration. It was difficult to discern that this tissue was markable except for a small area of healed tuberculosis in the apex of the right lung, and atelectasis of the lower lobe of the left lung. There was no fluid in the pleural cavities.

In the esophagus there were greatly dilated submucosal veins. Although no particular point

FIG. 5. A hepatoma attached to the wall of the right atrium. The tumor here was composed predominantly of spindle cells.

FIG. 6. A thrombus of pleomorphic hepatoma in a small branch of a pulmonary artery. These invaded vessels were constantly associated with the metastases of the tumor in the lungs.

derived from cells of the liver, but this type of anaplastic hepatoma is well recognized and often occurs in association with foci of better differentiated tumor. The tumor that invaded the inferior vena cava extended into the right atrium of the heart as is shown in Figure 4. There it formed a large mass, which combined with the associated thrombus on its surface, extended through the tricuspid valve and into the right ventricle. The orifice of the superior vena cava was not occluded and supplied the passageway by which venous blood returned to the heart after first draining through the usual collaterals of the portal and inferior vena caval systems. The histologic appearance of the tumor invading the atrium was considerably different from that in the section of the liver. As shown in Figure 5 it has a great many spindle cells which do not exhibit the degree of pleomorphism of the primary tumor. This, nevertheless, is also a histologic picture compatible with a hepatoma.

In the lung there were extensive metastases of this tumor, particularly at the base of the right lung. They were usually subpleural, and in the midst of the metastases there were often thrombi in the small branches of the pulmonary arteries. Figure 6 is a picture of one of these thrombi of tumor in a small pulmonary artery. The lungs were otherwise essentially unre-

of perforation was demonstrated, a rupture of one of these veins was considered the most likely source of the 2,200 ml. of fresh and altered blood found in the esophagus, the stomach and small intestines. There were also in the duodenum two ulcers which by both gross and microscopic examination showed little fibrous scarring, considerable edema, and sharp necrosis of tissue in their bases, changes indicative of acute and active ulcers. The hemorrhage did not appear to be associated with these ulcers, for there were no eroded vessels in their bases.

The kidneys showed a slight degree of arteriolarnephrosclerosis. The heart was slightly hypertrophied; it weighed 595 gm. including about 75 to 100 gm. of tumor. These observations can be interpreted as evidence of the probable previous existence of hypertension. There were no other lesions of significance in the kidneys. The degree of vascular disease seemed hardly enough to account for the elevation of non-protein nitrogen which was more likely due to the gastrointestinal hemorrhage rather than primary disease in the kidney. There was extensive arteriosclerosis of the aorta and coronary arteries with almost complete occlusion of the circumflex branch of the left coronary artery by an arteriosclerotic plaque. In the posterior wall of the left ventricle there was a large, healed infarct which by both

gross and microscopic examination showed no evidence of recent extension.

In conclusion, this patient had diffuse nodular cirrhosis of an advanced degree. The cause of this lesion in the liver cannot be stated because this is the anatomic end picture of a number of known causes of cirrhosis. Superimposed upon cirrhosis was a primary carcinoma of the liver which extended into the portal and hepatic veins, the inferior vena cava, and the right atrium of the heart. There were metastases only in the lung, and these were most marked subpleurally and particularly at the base of the right lung. The remainder of the alterations were essentially those that came about as a result of portal hypertension; namely, ascites, esophageal varices and the terminal event of rupture of one of the varices with massive gastrointestinal hemorrhage.

Anatomic Diagnoses: Diffuse nodular cirrhosis of the liver; primary carcinoma of the liver, hepatic cell type, with extension into the portal vein, hepatic veins, inferior vena cava and right atrium; metastatic carcinoma beneath the pleura of all lobes of the lung; esophageal varices; hemorrhage into the esophagus, stomach and intestines.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Reports

Reversible Metastatic Calcification Associated with Excessive Milk and Alkali Intake*

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METASTATIC calcification of various organs, the subcutaneous and periarticular tissues, first described by Virchow in 1855, may occur in a variety of conditions in which the blood serum is oversaturated with calcium and phosphorus.[1] It has been described in diseases associated with extensive destruction of bone and in the late stages of chronic renal insufficiency. Recently Burnett and his co-workers[2] have discussed a new type of metabolic disturbance in which metastatic calcification may occur. These authors reported six cases of calcinosis associated with long-standing peptic ulcer, mild hypercalcemia and renal insufficiency in which the metastatic calcification appeared to be related to the protracted ingestion of large amounts of milk and alkali. This syndrome, however, is not comparable to the findings in acute alkalosis.[3] The hypercalcemia in this group of cases is unlike that of primary hyperparathyroidism in that it is not accompanied with increased urinary excretion of calcium or hypophosphatemia.

Cases of metastatic calcification of the type described by Burnett are undoubtedly rare. Recently, we have observed a similar instance of widespread metastatic calcification associated with peptic ulcer and the prolonged ingestion of milk and alkali. The clinical picture was remarkably altered by dietary restriction of calcium intake, a feature that has not as yet been described.

CASE REPORT

E. B., a sixty-seven year old single white exseaman was admitted to Bellevue Hospital on February 1, 1949, with the complaints of abdominal pain and postprandial vomiting of several months' duration. Since 1928 he had been hospitalized intermittently for pulmonary tuberculosis. He had had a chronic productive cough, occasional blood-streaked sputum, shortness of breath and hoarseness for approximately one year. In 1936 he complained of intractable abdominal pain and repeated attacks of indigestion. A gastrointestinal study revealed a duodenal ulcer and the patient was placed on a Sippy regimen. These symptoms subsided, but during the following twelve to thirteen years he maintained a diet averaging 2 to 3 quarts of milk daily, supplemented by Sippy powders, antacids and alkalis. For eight or nine years his diet had consisted almost entirely of milk supplemented by an occasional egg. During the eighteen months prior to admission the patient had noted the gradual development of slightly painful swellings on his back, right shoulder and right wrist. For approximately two months he had noted progressive weakness, weight loss, anorexia and pruritus. He denied melena or hematemesis.

On physical examination the patient was a deaf, weak, emaciated, slightly confused elderly white male. His skin was dry and excoriated. At the inferior angle of each scapula was a nontender, cystic, rubbery mass measuring approximately 6 to 8 cm. in diameter, each one of which seemed attached to the underlying bone. Similar but more irregular masses were present at the right wrist and over the right acromioclavicular joint. There was no limitation of motion. A smaller, subcutaneous, fluctuant mass was noted over the proximal interphalangeal joint of the right fifth finger. Examination of the ocular fundi was negative. The cardiac findings were within normal limits. Blood pressure was 90/60 mm. Hg. Examination of the lungs revealed diminished resonance over the right apex posteriorly with an occasional wheeze and persistent medium moist crepitant rales. There was

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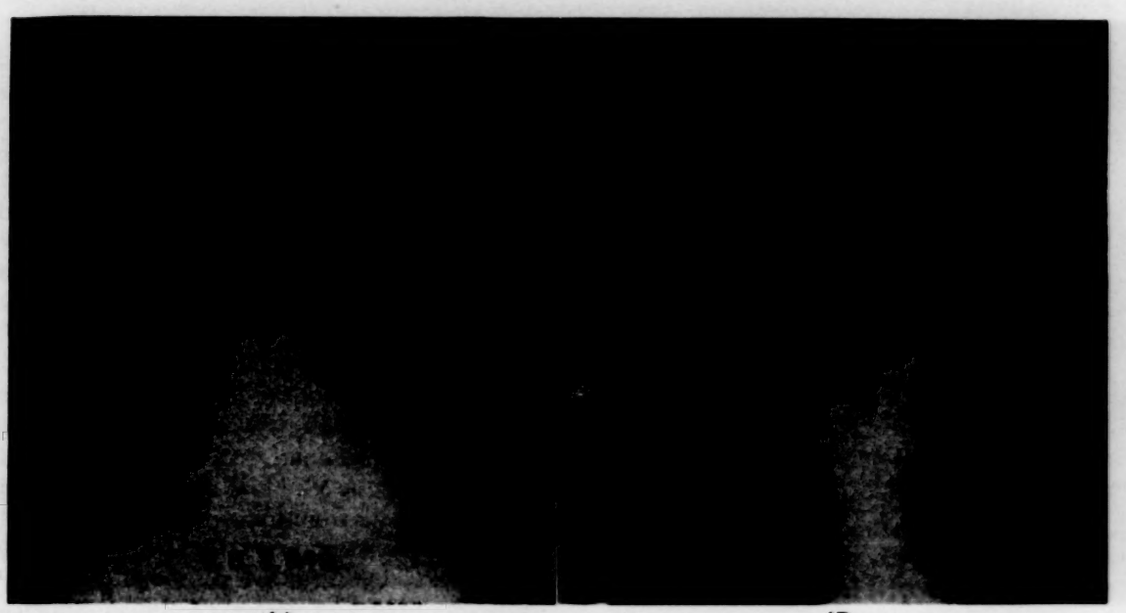


1A 1B

1C

FIG. 1. A, roentgenographic study of the chest on February 9, 1949, shows bilateral pulmonary tuberculosis, calcific masses attached to the inferior angles of both scapulae and a portion of the calcified mass at the right shoulder; B, a film of the right shoulder taken on February 6th demonstrates the calcific mass apparently arising in the region of the subacromial bursa; C, roentgenographic view of the right wrist on February 9th shows a calcific density in the region of the head of the ulna.

mild generalized abdominal tenderness. The prostate was slightly enlarged but was not tender and was of normal consistency.

Laboratory work-up revealed a negative serologic test for syphilis, hemoglobin 11 gm., red blood cells 3,190,000 per cu. mm. and a normal total and differential leukocyte count. Sputum concentrates were positive on two occasions for tubercle bacilli. Repeated urinalyses showed a low specific gravity ranging between 1.007 and 1.010, and on several occasions impaired ability to concentrate. There was a constant albuminuria and pyuria, the white cells occasionally occurring in clumps. Urine culture for pyogens showed a non-hemolytic staphylococcus aureus. Roentgenographic studies of the chest, right wrist and right shoulder are reproduced. (Fig. 1.) Repeated gastrointestinal barium studies showed an ulcer of the duodenal bulb. An electrocardiogram revealed auricular extrasystoles and changes thought to be compatible with an old anterior wall infarction. The Q-T interval was normal. Phenolsulfonphthalein excretion was less than 5 per cent. Blood urea nitrogen varied between 58 and 61 mg. per cent, and the alkaline phosphatase 3 to 5 Bodansky units. On several occasions the serum calcium ranged between 10.8 and 11.8 mg. per cent, and the serum phosphorus between 3 and 5 mg. per cent. Acid phosphatase was 1 King-Armstrong unit, the serum cholesterol 230 mg. per cent and total serum proteins 7.2 gm. per

FIG. 2. Microscopic section of subcutaneous mass removed from the angle of the scapula. Calcium deposition in a grumous eosinophilic matrix surrounded and traversed by fibrous tissue. Just within the capsule there is a mononuclear and foreign body giant cell reaction; hematoxylin and eosin, × 6.

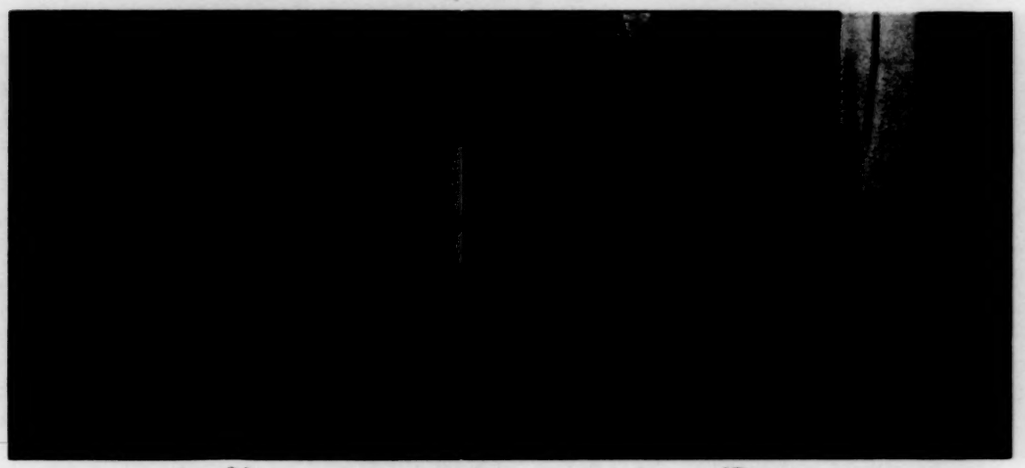
cent, with an albumin-globulin ratio of 4.9/2.3. The Sulkowitch test was normal and a quantitative analysis of urinary calcium excretion revealed an excretion of 0.312 gm. in forty-eight hours. The CO_2 combining power varied between 14 and 38 volumes per cent.

The patient was initially ambulatory and afebrile. He was placed on a regular diet with antacids and antispasmodics to control his vomiting and abdominal pain but he continued to have gastrointestinal complaints which were relieved only when a Sippy regimen was reinstituted. On March 1, 1949, an excisional biopsy of the tumor mass at the angle of the right scapula was performed under local anesthesia. The tumor was found to be cystic, contained thin seropurulent material and was adherent to the periosteum of the right scapula. Microscopic examination revealed spherules of calcium deposited in a grumous eosinophilic matrix. The mass of tissue was encapsulated and traversed by fibrous strands. The inner surface of the capsule was lined by mononuclear phagocytes and giant cells of the foreign body type. The pathologic diagnosis was calcium gout. (Fig. 2.) Intravenous pyelograms failed to show any dye excretion. In June, 1949, slit lamp examination revealed minute, crystal-clear, oval conjunctival lesions, some singly and others in clusters, in the right temporal bulbar conjunctiva together with bilateral corneal changes resembling a band keratitis.* During this same month the patient was taken off a Sippy regimen and placed on a Meulengracht or regular diet as tolerated. Milk and absorbable alkalies were eliminated from his diet as much as possible. Because of the gradually increasing dysuria and frequency and difficulty in urination a transurethral resection of the medium bar of the prostate gland was performed in August. Following this procedure the urinary symptoms subsided although there was no reduction in the blood urea nitrogen. The patient's convalescence was complicated on September 3rd by a sudden massive hematemesis of approximately 400 cc. He responded well to several transfusions.

Following the elimination of milk and absorbable alkalis from the patient's diet there was a gradual resorption of the previously noted masses at the right wrist, shoulder and left scapula. (Fig. 3.) However, blood chemistry studies showed no significant changes. The blood urea nitrogen ranged between 40 and 62 mg. per cent, the serum calcium 9.17 and 13.1 mg. per cent, serum phosphorus 1.9 and 4.0 mg. per cent, and the alkaline phosphatase between 2.0 and 3.5 Bodansky units. There was no improvement in phenolsulfonphthalein excretion. The Sulkowitch test remained negative and on December 29th the urinary calcium excretion was 71.8 mg. in twenty-four hours. Urinary findings and the anemia persisted. A follow-up ophthalmologic examination revealed that the band keratitis was still present but that the glass-like, clear conjunctival deposits noted earlier had disappeared. During November and December the patient began to have increased episodes of vomiting and abdominal pain which were controlled only by demerol, milk and aluminum hydroxide. He suffered from persistent vomiting, inability to retain solid food, gradually increasing disorientation and markedly increased weakness despite adequate parenteral vitamins and nourishment. On March 1, 1950, the blood urea nitrogen had risen to 122 mg. per cent. Serum phosphorus was 5.2 mg. per cent, serum calcium 9.17 mg. per cent, blood creatinine 2.1 mg. per cent and plasma chlorides 85.2 mEq./L. The patient's condition showed rapid deterioration. Despite small feedings by Levine tube, which he was able to tolerate without vomiting, his condition became progressively worse and he expired on March 9th.

Autopsy examination was performed approximately four hours after death. Only the

* Similar changes were noted in Burnett's cases and have been described in the literature.[4]



3A 3B

FIG. 3. A, detailed view of the right shoulder taken October 10, 1949. The calcium deposits have been almost completely resorbed; B, similar resorption is demonstrated in a film of the right wrist taken on October 18th.

pertinent gross and microscopic findings are included:

The body was that of an emaciated elderly white male. There was a 2 cm., soft, movable subcutaneous mass over the left scapula and there were several small plaque-like thickenings of the skin over the upper back. On opening the chest numerous fibrous adhesions were noted over the upper third of both lungs. The cardiac findings were within normal limits; the coronary arteries were patent and not sclerotic. A moderate amount of atherosclerosis was present throughout the aorta with areas of ulceration and thrombi formation in the abdominal portion. The renal arteries were not stenosed or sclerotic. The lungs were crepitant throughout with a nodularity of the right upper lobe on palpation. The bronchi were not dilated. There were numerous fibrocaseous foci throughout the right upper lobe, in the upper half of the right middle lobe and in the apex of the left upper lobe. Several irregular cavities measuring from 0.5 to 0.1 cm. in diameter were present in the right upper lobe. The parathyroid glands measured 0.4 to 0.8 cm. in diameter.

The kidneys each weighed 90 gm. without the capsules. They were small and soft. The capsules stripped with difficulty leaving a coarsely granular reddish surface. The cortex measured 0.4 cm. The pyramids were distinct and contained short streaks of firm yellow material which appeared to follow the tubular pattern. The cut surface was purplish red in color.

The stomach contained 200 cc. of watery gray fluid and was not dilated. The mucosa appeared slightly injected but the pattern of the folds was normal. The muscularis was not hypertrophied. The pyloric canal measured approximately 1.0 cm. in diameter and admitted a forefinger without difficulty. There was no evidence of mechanical obstruction. One-half centimeter distal to the pylorus was an ulcer crater on the posterior wall of the duodenum measuring 1 cm. in diameter and 0.3 cm. in depth. The base was gray and red and in the center contained the open end of a thick-walled blood vessel measuring 0.3 cm. in outside diameter. This vessel was sclerotic and the lumen was obstructed a few millimeters from the open end. The ulcer and surrounding duodenum were intimately adherent to a firm mass of pancreas. In the distal 8 feet of ileum there were five shallow ulcers varying from 0.3 to 1.0 cm. in diameter. The long axis of these ulcers was at right angle to the long axis of the ileum. On the serosal surface opposite these ulcers were several small yellow tubercles. The ileum and colon contained soft, black tarry feces.

Exploration of the right shoulder region revealed no lesion. The subacromial bursa was free of scarring or calcification.

Sections of the heart revealed only a few small areas of myocardial fibrosis. Sections through the grossly nodular areas in the lung revealed extensive fibrosis and organization of the pulmonary parenchyma. Within these areas there were numerous epithelioid tubercles con-

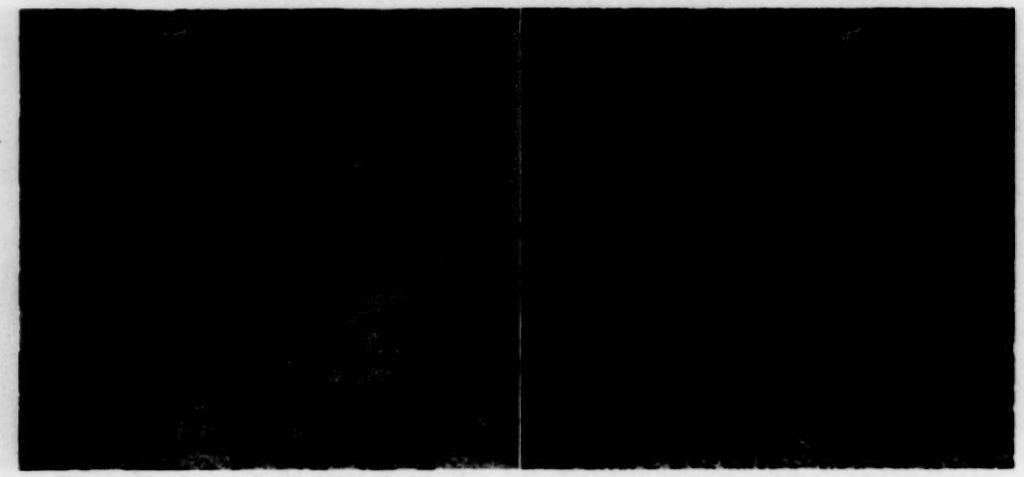


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FIG. 4. Microscopic section of lung. There is metastatic calcification in the form of plates and bars of calcium within the alveolar septa. Calcium is stained black; von Kossa stain, × 144.

FIG. 5. Microscopic section of kidney. Note the partial hyalinization of glomeruli and the fibrous thickening of Bowman's capsule. The black masses are deposits of calcium involving the tubular cells and the lumina of the tubules; von Kossa stain, × 144.

taining Langhans type giant cells and several larger areas of caseous necrosis surrounded by tuberculous granulation tissue. There were scattered foci of lymphocytes. Many of the alveoli which remained were filled with a polymorphonuclear exudate and phagocytes. In some areas the exudate became confluent and small abscesses were present. Many of the bronchi were also filled with polymorphonuclear cells. The pleura was thickened and fibrous adhesions were present. The striking feature was the presence of parenchymal calcification most prominent at the periphery of the zones of tuberculous pneumonia but involving groups of alveoli which were otherwise normal. The calcification was in the form of small nodules or linear streaks which outlined the alveolar septa and surrounded the small bronchi and vessels. (Fig. 4.) The degree of calcium deposition within the older caseous foci was not abnormal.

The liver showed mild portal cirrhosis with an increase in portal fibrous tissue, together with lymphocytic infiltration and slight proliferation of the bile ducts. Fibrous septa extended from the portal areas dividing the parenchyma into irregular lobules. There was some regeneration of the portal cells but isolated groups of liver cells in the portal areas showed atrophy.

The renal capsule was thickened. Numerous glomeruli showed partial to complete hyalinization and thickening of Bowman's capsule was a prominent feature. In the areas of glomerular hyalinization there was marked tubular atrophy with increase in the interstitial connective tissue in which a diffuse lymphocytic infiltration was seen. The more normal tubules were dilated and hypertrophied. The striking feature was the extensive calcification of renal convoluted tubular cells and in some cases the deposition of calcium masses in tubular lumina. (Fig. 5.) This extended to the collection tubules. Large aggregates of calcium were seen beneath and bulging into the calyceal mucosa. The arterioles were not prominent. There was some intimal thickening of the small and medium-sized arteries.

There was some testicular atrophy and increased fibrosis.

Sections from the ileum revealed a sharply demarcated ulceration with overhanging mucosal edges. The floor of the ulcer consisted of tuberculous granulation tissue. There were a lymphocytic and plasma cell infiltration and many small foci of caseation necrosis surrounded by epithelioid cells and Langhans type giant cells. The tubercles were present in the submucosa, muscularis and subserosa.

Sections of the parathyroid glands revealed a normal-appearing parenchyma with a prominence of chief cells and occasional small clusters of oxyphil cells. Many of the chief cells were of the water-clear type. The bone marrow was normal. An occasional lacuna was seen but

there was no evidence of any marked osteoclastic activity.

Final anatomic diagnosis: (1) chronic ulcer of duodenum with erosion of superior pancreaticoduodenal artery; (2) metastatic calcification in lung, kidneys and subcutaneous tissue (biopsy); (3) chronic glomerulonephritis; (4) hyperplasia of parathyroid gland, mild; (5) tuberculosis of lungs with cavity formation, bilateral; (6) tuberculosis of ileum; (7) fibrous pleural adhesions, bilateral; (8) atherosclerosis of aorta with calcification, ulceration and thrombus formation; (9) portal cirrhosis, mild; (10) atrophy and fibrosis of testis.

COMMENT

The case reported herein appears to fall into the group of metastatic calcification described by Burnett. In order to establish the criteria by which this syndrome can be recognized a detailed review of the various types of metastatic calcification is pertinent.

Metastatic calcification, by definition, occurs in normal tissues, in contrast to the dystrophic calcification of previously injured tissues. As already indicated, oversaturation of the serum with calcium and phosphorus is the chief prerequisite for the occurrence of metastatic calcification. There are, however, a few rare cases of so-called tumoral calcinosis indistinguishable clinically and pathologically from true metastatic calcification in which the mineral constituents of the blood are not altered.[5] Although abnormal calcification associated with scleroderma has sometimes been classified as an example of metastatic calcification, it should more properly be grouped with the dystrophic variety since the sites of calcium deposition are in previously altered collagen. Myositis ossificans is also a dystrophic rather than a metastatic type of calcification.

Metastatic calcification associated with elevation of serum calcium and phosphorus can be subdivided into (1) cases with hyperparathyroidism and (2) cases with normal parathyroid function.

Among the first group are (1) cases of primary hyperparathyroidism and (2) cases of secondary hyperparathyroidism associated with chronic renal disease and long-standing renal insufficiency. Nephrocalcinosis may result from primary hyperparathyroidism without pre-existing renal disease.[6] If renal calcification proceeds to the stage of impaired renal function, hyperphosphatemia as well as hypercalcemia may develop and favor gross metastatic calcification. Hypercalcemia *per se* does not ordinarily suffice to cause metastatic calcification. The reported cases of primary hyperparathyroidism, with metastatic calcification, invariably have been in severe renal failure with hyperphosphatemia for a prolonged period.[7–9] Under these conditions it may be impossible to distinguish clinically between primary and secondary types of hyperparathyroidism although the degree of hypercalcemia is generally greater in primary hyperparathyroidism. In both categories a vicious cycle is established in which renal damage leads to phosphate retention and further parathyroid hyperplasia, which in turn increases the degree of hypercalcemia. In both primary and renal hyperparathyroidism the occurrence of gross metastatic calcification indicates that not only have both the serum calcium and phosphorus been increased but also that the disease has reached an irreparable final stage even though death from uremia may be delayed for years.

Metastatic calcification with normal parathyroid function can occur only if there is an oversupply of calcium and phosphorus that reaches the blood from endogenous or exogenous sources. Three main groups are recognized: (1) massive destruction of bone by tumors such as multiple myeloma, (2) vitamin D_2 poisoning and (3) excessive intake of calcium, as in the case described herein.

When metastatic calcification results from extensive destruction of bone,[10] there is usually both hypercalcemia and hyperphosphatemia although sometimes there may be hypophosphatemia, similar to the finding in the early stages of primary hyperparathyroidism.[11]

In vitamin D_2 overdosage, increased absorption of calcium and phosphorus from the intestinal tract as well as from the bones is the mechanism of hypercalcemia, which may lead to renal calcification, nitrogen retention, hyperphosphatemia, osteoporosis and metastatic calcification. A prolonged intake of excessive vitamin D_2 is usually required to produce this syndrome.

Hypercalcemia produced by excessive calcium intake, as described by Burnett and as seen in the present case, has been observed only after the prolonged ingestion of large amounts of milk and concomitant alkali. A prodigious degree of calcium consumption is apparently required. In our patient 5 gm. of calcium were

consumed daily, the normal daily requirement being only 1 gm. per day. It appears reasonable, therefore, to attribute the metastatic calcification in these cases to an abnormally high intake of calcium. Vitamin D_2 is not an important factor for even if the milk that was consumed in our case was fortified with this ingredient the daily consumption would be only about 400 units. This might increase the absorption of calcium and phosphorus somewhat but could hardly lead to metastatic calcification. The role of the associated alkali intake is not evident but apparently no cases of this syndrome have been observed in which only excessive milk or excessive alkali alone were consumed.

The role of the kidneys in metastatic calcification appears to be the same in all cases whether or not hyperparathyroidism is a factor. Renal calcification can occur in all forms of hypercalcemia, presumably due to an increased concentration of calcium in the glomerular filtrate. Renal calculi, caused by massive excretion of calcium, with accompanying pyelonephritis may contribute to the development of renal failure in these cases. Impairment of renal function as a consequence of tubular calcification can lead to retention of phosphate in the serum. Metastatic calcification in extrarenal tissues then results because of the oversaturation of the blood with these two electrolytes. In our case it must be assumed that the initial phase consisted of temporary periods of increased serum calcium due to the drinking of large amounts of milk and that this effect was analogous to the persistent hypercalcemia of primary hyperparathyroidism.

In our own case the pre-existing renal lesion may have facilitated the development of metastatic calcification. There is evidence, however, that the syndrome may occur even if the renal parenchyma is previously undamaged. For example, severe renal damage can result from overdosage with vitamin D_2 in patients with previously normal renal function. In such instances there may be restoration of normal renal function when the vitamin consumption is stopped.[12] In one of Burnett's cases a renal biopsy was performed during the course of a sympathectomy for hypertension three years prior to onset of the syndrome. This revealed normal renal tissue. In other cases renal function returned to normal when the patients discontinued the milk diet. This is in sharp contrast to our own case in which renal failure was progressive. Renal failure of hyperparathyroid origin also is irreversible even if parathyroid tumors are successfully removed.

The extent of metastatic calcification is in general directly proportional to the severity of the underlying metabolic disturbance. In only one of Burnett's cases was there grossly detectable metastatic calcification. In the other five only microscopic calcification of the kidneys, lungs, blood vessels and heart were noted.

The metastatic calcification associated with vitamin D_2 poisoning has been observed to disappear when therapy is instituted before the condition has progressed too far. The metastatic calcification resulting from excessive dietary intake of calcium, as indicated by the observations in the present case, is also reversible when therapy is instituted in time. The indications from our observations are that calcium salts may be resorbed with ease from the subcutaneous and periarticular tissues but may be less resorbable from other tissues. This does not preclude the possibility that restoration of function may not be achieved in calcified organs with suitable therapy.

Although, in retrospect, the present case appears to be one of metastatic calcification, at the time of admission the patient presented a difficult diagnostic problem. Radiologic absence of extensive bone destruction made it unlikely that the metastatic calcification was due to multiple myeloma, metastatic cancer or primary hyperparathyroidism. The osteoporosis of vitamin D_2 poisoning[12,13] was also lacking. The high urea nitrogen of the blood suggested that secondary renal hyperparathyroidism might be present but this was ruled out by the normal serum phosphorus. The very mild elevation of serum calcium was against primary hyperparathyroidism with secondary renal calcinosis. The normal alkaline phosphatase and normal urinary excretion of calcium also were against the diagnosis of hyperparathyroidism. When the observations of Burnett and his associates were called to our attention, it was at once apparent that the case belonged to this new syndrome of metastatic calcification following excessive dietary intake of milk and alkali.

SUMMARY

A case of metastatic calcification secondary to a prolonged intake of milk and alkali is presented. Regression of ocular and subcutaneous lesions was noted following dietary restriction of calcium although the patient subsequently

died in renal insufficiency. The pathogenesis of the various forms of metastatic calcification is reviewed.

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REFERENCES

1. Herbert, F. K., Miller, H. G. and Richardson, G. O. Chronic renal disease, secondary parathyroid hyperplasia, decalcification of bone and metastatic calcification. *J. Path. & Bact.*, 53: 161–181, 1941.
2. Burnett, C. H., Commons, R. R., Albright, F. and Howard, J. C. Hypercalcemia without hypercalcuria or hypophosphatemia, calcinosis and renal insufficiency. *New England J. Med.*, 240: 787–794, 1949.
3. Grace, W. J. and Barr, D. P. Complications o alkalosis. *Am. J. Med.*, 4: 331–337, 1948.
4. Walsh, F. B. and Howard, J. E. Conjunctival and corneal lesions in hypercalcemia, *J. Clin. Endocrinol.*, 7: 644–652, 1947.
5. Thomson, J. E. M. and Tanner, F. H. Tumoral calcinosis. *J. Bone & Joint Surg.*, 31 A: 132–140, 1949.
6. Parsons, W. B. Results of operations for hyperparathyroidism. *Bull. New York Acad. Med.*, 25: 285–297, 1949.
7. Hanes, F. M. Hyperparathyroidism due to parathyroid adenoma with death from parathormone intoxication. *Am. J. M. Sc.*, 197: 85–90, 1939.
8. Rogers, H. M. Parathyroid adenoma and hypertrophy of parathyroid glands. *J. A. M. A.*, 130: 22–28, 1946.
9. Ballin, D. E. and Gershwin, B. S. Hyperparathyroidism with renal insufficiency. *Am. J. M. Sc.*, 190: 519, 1935.
10. Swyer, A. J., Berger, J. S., Gordon, H. M. and Laszlo, D. Hypercalcemia in osteolytic metastatic cancer of the breast. *Am. J. Med.*, 8: 724–732, 1950.
11. Albright, F. and Reifenstein, E. C., Jr. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams & Wilkins Co.
12. Steck, I. E., Deutsch, H., Reed, C. I. and Struck, H. C. Further studies on intoxication with vitamin D. *Ann. Int. Med.*, 10: 951–964, 1937.
13. Christensen, W. R., Liebman, C. and Sosman, M. C. Skeletal and periarticular manifestations of hypervitaminosis D. *Am. J. Roentgenol.*, 65: 27–41, 1951.

Vitamin D Poisoning with Metastatic Calcification*

Report of a Case and Review of the Mechanism of Intoxication

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LARGE doses of vitamin D preparations have been administered mainly on an empirical basis for the treatment of a wide variety of diseases, including arthritis of various types, pollinosis, tetany, psoriasis, acne and trichinosis. The dangers associated with administration of these preparations, which are potentially toxic, have been widely publicized in the medical literature but unfortunately too often have not been considered seriously enough by many doctors or their patients.

This case is presented with the purpose of re-emphasizing the outstanding clinical signs and the chemical, tissue and skeletal changes that occur in the syndrome of vitamin D poisoning. The practice of uncontrolled self-medication with Nion D (activated ergosterol) proved to be hazardous in this patient by producing chronic renal insufficiency and metastatic calcification in the soft tissues.

CASE REPORT

M. C. P. is a sixty-two year old white male who has had rheumatoid arthritis of the spine and many peripheral joints for the past twenty years. He remained in his occupation as a carpenter until twelve years ago when he became incapacitated due to increase in the severity of the disease. He was seen at the Veterans Administration Hospital for the first time on March 20, 1948, and was treated for subarachnoid hemorrhage. The blood pressure on admission was 240/120 and subsided to 130/80 prior to discharge on May 25, 1948. Laboratory data at this time revealed a red blood count of 3,400,000 and hemoglobin of 10 gm. per cent, blood urea nitrogen of 28 mg. per cent and CO_2 combining power of 58 volumes per cent. Urinalysis showed specific gravity varying from 1.008 to 1.018 with a trace of albumin, 2 white blood cells and an occasional hyaline and granular cast per high power field.

After discharge from the hospital he continued to have pain over the right side of the head and returned for observation in October, 1948, for a period of three weeks. The patient also complained of frequency of urination and nocturia of four to five times. Laboratory data revealed a red blood count of 4,100,000 and the urinalysis showed a specific gravity of 1.012 with no albumin and a normal urinary sediment. No specific cause for the headache was found.

He did not return to the hospital until January 27, 1950, at which time he complained of generalized aches and pains which were not limited to the joint areas. He had the same urinary symptoms. The patient stated that swelling of the left index finger had been present for about two months. Also he had been aware of a painful mass in the right hip for about six months. His appetite was fair and there was no history of loss of weight. He admitted to infrequent nausea and vomiting but otherwise there seemed to be no significant gastrointestinal symptoms. There was a feeling of tightness across the occipital area and pain in the costovertebral angles.

Physical examination revealed a chronically ill, sallow, poorly nourished, white male in no acute distress. Temperature was 98.6°F., pulse 90, respirations 20 and blood pressure 140/88.

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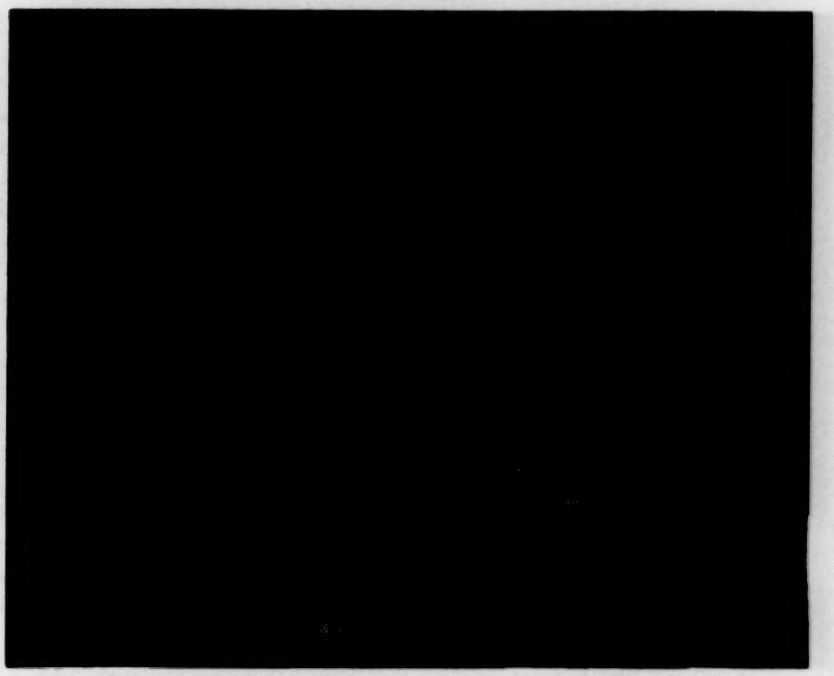

FIG. 1. Right hand showing calcification in the soft tissue about the proximal interphalangeal joint of the index finger; left hand showing calcification in the soft tissue about the proximal interphalangeal joint of fifth finger.

There was grade I arteriosclerotic retinopathy and evidence of a moderately severe inactive rheumatoid arthritis of long-standing involving multiple joints. A fluctuant mass was present on the proximal interphalangeal joint of the right index finger and the distal interphalangeal joint of the left fifth finger, each measuring approximately 1.5 cm. in diameter. There was also a tender, firm, freely movable mass in the right buttock approximately 9 by 6 cm. in size.

During this period of hospitalization it was noted for the first time that the patient had marked renal insufficiency and metastatic calcifications were evident on x-ray. The laboratory reported a red blood count of 4,100,000, hemoglobin 11.5 gm. per cent, white blood count 6,000 and sedimentation rate 27. The urinalyses showed specific gravities varying from 1.007 to 1.012, albuminuria and a few white blood cells, red blood cells and an occasional hyaline granular cast per high power field. During his hospital stay the blood urea nitrogen dropped from 82 to 46 mg. per cent and the CO_2 combining power increased from 27 to 49 volumes per cent. The serum calcium was 13.5 mg. per cent and the serum inorganic phosphorus was 4.1 mg. per cent. The Mosenthal concentration test showed the highest specific gravity to be 1.012 and the intravenous pyelogram revealed a markedly delayed excretion by the kidneys. X-ray of the hands showed a calcified mass around the proximal interphalangeal joint of the right index finger and at the distal interphalangeal joint of the left fifth finger. (Fig. 1.) An x-ray of the right hip showed a moderately dense non-homogenous calcified mass measuring 9.0 cm. in the greatest diameter in the region of the neck and greater trochanter of the femur. (Fig. 2.)

With this information, further questioning of the patient revealed that he had taken Nion D, 4 capsules daily (50,000 units vitamin D in each capsule), from 1942 to 1948. At that time he discontinued the drug on the advice of his family doctor in spite of the fact that he had obtained marked symptomatic relief of his rheumatic complaints. It is also interesting that he had been on an average diet throughout life, drank only one to two glasses of milk weekly and rarely took cheese or cream.

While in the hospital the mass in the left index finger was aspirated and 5 cc. of thick, white, chalky material was obtained. Chemical analysis showed the material contained calcium, 25 mg. per cent, and uric acid, 2 mg. per cent. Microscopic examination revealed innumerable white blood cells. With the above information a diagnosis of vitamin D poisoning was made. The

FIG. 2. Right hip showing multilocular calcification.

patient was discharged in May, 1950, to return at frequent intervals for re-evaluation with the advice that he continue on low calcium diet and abstain from the use of drugs containing vitamin D.

On readmission two months later there was no significant change in his status. He had remained on low calcium diet and the aspirated joint had not refilled. X-ray of the right hip showed no increase in the size of the mass. There was no change in the blood count; however, the blood urea nitrogen remained elevated at 64 mg. per cent and the serum calcium at 12.1 mg. per cent.

He was readmitted for the fifth time in August, 1950, complaining of pain in all the joints. All laboratory studies were the same except for the blood urea nitrogen which was now 45 mg. per cent.

On readmission in January, 1951, he complained of dizziness and weakness of three months' duration. He had gained 5 pounds in weight and for the first time demonstrated pitting edema of the feet and legs of moderate severity. Laboratory studies showed red blood count 3,400,000 and hemoglobin 10.4 gm. per cent, blood urea nitrogen 27 mg. per cent, CO_2 combining power 45 volumes per cent, serum calcium 10 mg. per cent and a serum protein of 5.7 with albumin 3.4 and globulin 2.3 gm. per cent. The patient was given a low sodium, low calcium diet, ferrous sulfate gr. 5 three times a day and 1 blood transfusion. Kidney function remained very poor as evidenced by inability to concentrate the urine beyond a specific gravity of 1.012. A PSP test revealed that the patient had a total excretion of 18 per cent over a two-hour period. The intravenous pyelogram continued to show a marked delay in excretion.

He was readmitted in February, 1951, with the chief complaint of severe pain down the right leg which was aggravated by change of position and was becoming progressively more severe. There was no apparent change in the mass in the right buttock either on physical or x-ray examination. At this time the serum calcium was 10.3 mg. per cent, serum inorganic phosphorus 4.4 mg. per cent and serum alkaline phosphatase 1.8 Bodansky units. Serum protein was 6.5 with albumin 3.7 and globulin 2.8 gm. per cent. The urine continued to show specific gravity of 1.011, a trace of albumin and a few red blood cells, white blood cells and casts per high power field. A Sulkowitch test revealed a normal excretion of calcium. The hands were x-rayed and showed disappearance of the calcium deposits around the finger joints reported one year previously. (Fig. 3.)

In spite of poor kidney function it was deemed advisable to remove this mass which was obviously causing traumatic sciatic neuritis. On March 12, 1951, a large nodular multiloculated cystic mass, measuring 10 by 6 by 3 cm., was found lying beneath the gluteus maximus muscle and extending laterally over the right hip joint adjacent to the trochanteric bursa but not originating in the bursa. (Fig. 4.) Chemical analysis of the contents of the cysts showed calcium 18.4 per cent and phosphorus 7.1 per cent, about the same proportion found in normal bone.

The pathologic report was as follows: Gross examination revealed that the specimen consisted of a mass of tissue measuring 10 by 7 by 5 cm. The external surface was shaggy, brown and was studded by small pale yellow nodules. The tissue grated on the knife when it was cut. Gross section revealed loculated and conglomerate, dense deposits of a gritty, oily, pale yellow material. Microscopically, the section presented a mass of tissue in which there were numerous deposits of a foreign material con-

FIG. 3. Both hands showing absence of calcifications demonstrated in Figure 1 (one year later).

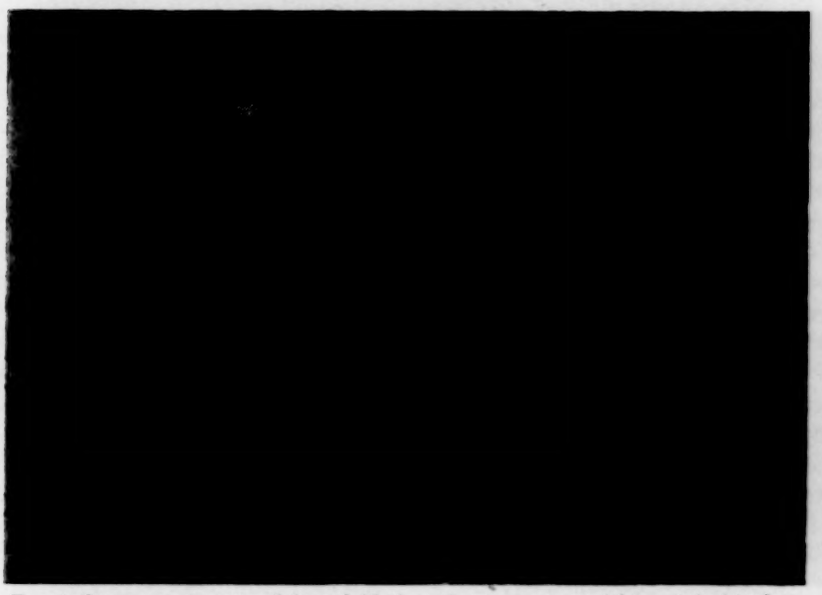

FIG. 4. Gross appearance of the calcified cystic mass removed from right hip (cut section).

taining calcium. The deposits were rimmed and separated by fibrocollagenous connective tissue which contained great numbers of foreign body giant cells and was infiltrated by lymphocytes and plasma cells. There were also groups of macrophages laden with golden brown pigment.

Other examinations at this time included fluoroscopy and x-ray of the stomach inflated with air in an effort to demonstrate calcification which was unsuccessful. Flat and Bucky films of the abdomen to demonstrate calcification in the kidneys were negative.

COMMENTS

This case report of vitamin D poisoning following the intake of Nion D* (activated ergos-

* Manufactured by Nion Corporation, Los Angeles, Calif.

terol) is important in presenting the outstanding clinical signs; the impairment of renal function and degenerative lesions with vicarious calcification. The outstanding symptoms in this case were frequency of urination and nocturia four to five times.

In the majority of approximately 120 cases reported of intoxication with vitamin D in the past twenty years, many gastrointestinal and systemic symptoms have been noted. Howard and Meyer[1] recorded ten cases complaining of weakness, fatigue and lassitude. Eight of these patients had severe anorexia, nausea and vomiting and in seven polyuria, polydypsia and nocturia were present. Reed, Struck and Steck[2] were also impressed with this symptomatology in their cases and stated that severe anorexia was usually the first symptom. They studied sixty-three cases of vitamin D poisoning and found that thirteen noted a tightness across the occiput which was followed by an increase in sensitivity of the skin of that area. One of these observers was so impressed that he took 35,000 units of vitamin D per kg. of body weight and also felt this sensation.

There is a great variation in species susceptibility and individual susceptibility to the toxic action of vitamin D. Steck and his associates[2] found that both human subjects and dogs generally survive administration of 20,000 units per kg. per day for indefinite periods without intoxication. Yet Reed and his associates[2] have reported toxic effects in one adult with as little as 1,000 international units per kg. of body weight daily. They also found that toxicity was more likely to occur in patients with gastrointestinal dysfunction. In the series reported by Howard and Meyer[1] the patient receiving the largest daily dose, 600,000 i.u., became ill earliest, but the one receiving the next highest dose, 500,000 i.u., did not manifest symptoms until he had taken the drug for eighteen months. Our patient took approximately 200,000 i.u. of Nion D daily for four of every six weeks for seven years. During the seventh year evidences of renal impairment were found and fifteen months later the sites of metastatic calcification were discovered and hypercalcemia was still present. These findings were also noted in a case reported by Howard and Meyer[1] in which hypercalcemia and an elevated nonprotein nitrogen were present fourteen months after withdrawal of the drug.

The mechanism of intoxication with vitamin D remains obscure; however, it is an interesting field for speculation. The concepts of vitamin D poisoning have been summarized by Albright and Reifenstein[4] from the metabolic data on their patients. It was established twenty years ago by Bauer, Marble and Claflin[5] that the administration of 30 mg. of irradiated ergosterol to normal individuals daily resulted in a decrease in the fecal calcium and phosphorus excretion and a concomitant increase in the excretion in the urine, with little change in the serum calcium and phosphorus. These results have also been obtained in a patient with osteomalacia secondary to steatorrhea.[4] The decreased fecal calcium excretion is the result of increased calcium absorption from the bowel, which probably represents the first action of vitamin D. A subject with idiopathic hypoparathyroidism with a low serum calcium was chosen and it was noted that administration of 540 mg. of calcium intravenously did not result in the appearance of calcium in the urine immediately and there was no appreciable change in the fecal calcium excretion. However, after oral administration of an equal amount of calcium there was a markedly increased fecal calcium excretion which, in turn, decreased after giving vitamin D. It was concluded that these findings were due to increased absorption of calcium and not to decreased re-excretion into the gastrointestinal tract.[4] This increased calcium absorption from the gut results in hypercalcemia and hypercalciuria. This was noted by Albright and Reifenstein[4] in their metabolic study on a patient with rickets, slightly resistant to vitamin D, who after receiving large doses of the drug showed an increase in the calcium in serum and urine. That the increase in the serum calcium in vitamin D intoxication may be due, at least in part, to the mobilization of calcium from the bones seems quite definite according to the several investigators. Hess, Weinstock and Rivkin[6] administered irradiated ergosterol to infants and animals with rickets and tetany and raised the serum calcium and inorganic phosphorus to normal levels, and on administration to normal infants and animals it produced a hypercalcemia. In an effort to determine the source of the calcium, rats were placed on a diet low in calcium and high in phosphorus for three days until there was no calcium in the feces and the serum calcium had been reduced from 10 mg. to 6.4 mg. per 100 cc. serum. The rats were given 1 mg. of irradiated ergosterol daily and

the serum calcium increased 50 per cent or more. The same workers[7] in another study found that the ash of bones of rats receiving large doses of irradiated ergosterol was lower than that of the control animals and concluded again that the source of the calcium was in the tissue, more particularly the bones which are the great storehouses of calcium in the body. If the dose of irradiated ergosterol is 100 times the therapeutic dose, the calcium will be withdrawn even from the bones of parathyroidectomized animals. These conclusions have been supported by many other workers and more recently by McLean[8] who believes that ordinary antirachitic doses of vitamin D increase absorption of calcium and probably phosphate from the gastrointestinal tract; however, massive doses of the drug give a result in increased mobilization of the bone salt. Vogt and Tønsager[9] administered vitamin D_2 to five cases of lupus vulgaris and examination of bone revealed a slight loss of calcium.

It has been postulated by many that vitamin D has a second action which is apparent only in the study of people without intact or functioning parathyroid glands. Albright and Sulkowitch[10] found that administration of vitamin D to three cases of idiopathic hypoparathyroidism resulted in an increase in the urinary phosphorus excretion greater than could be explained by the decreased fecal excretion, thereby inducing a state of negative phosphorus balance. However, administration of vitamin D to a patient with rickets, who was quite resistant but not intractable to therapy, resulted in an increase of serum calcium and phosphorus and an increase in urinary calcium but no increase in the urinary phosphorus excretion. The metabolic studies as stated offer some evidence that the rise in serum inorganic phosphorus which usually follows vitamin D therapy is the result of an accompanying decreased activity of the parathyroid gland. Harrison and Harrison[11] have supported this latter conclusion in dogs maintained on rachitogenic diets. Here vitamin D administration resulted in a marked increase in the maximal rate of tubular phosphate reabsorption, thus increasing the inorganic phosphate in the plasma. The injection of parathyroid hormone resulted in a marked decrease in the maximal rate of reabsorption of phosphates by the tubules. Therefore, it is believed that the second action of vitamin D is entirely masked by the first effect in a patient with intact parathyroids, as seen in our case report. According to Albright and Reifenstein[4] the most probable sequence of events in the average patient taking vitamin D would be (1) increased calcium absorption, (2) increased serum calcium level, (3) decreased parathyroid activity, (4) decreased urinary phosphorus excretion, (5) increased serum phosphorus level, (6) therefore decreased resorption of bone, causing a fall in serum and urinary calcium level, thus offsetting the effect of absorption of calcium from the gastrointestinal tract. On the other hand, with poisoning by vitamin D and a resultant excess of the first action of the drug, we have a supersaturation of the blood with respect to calcium phosphate and a precipitation of calcium phosphate at abnormal sites.

The occurrence of metastatic calcification is the most severe toxic effect. It is one of the characteristic findings in animals poisoned with vitamin D and the kidney is frequently the site of these deposits. Ashford[12] demonstrated that metastatic calcification, produced experimentally in rabbits, underwent resorption after vitamin D was discontinued. McLean and Lebo[13] reported a case in which calcification of the periarticular areas of fingers resorbed after discontinuing the drug and this observation was also made in our case; however, the kidney damage which follows the deposition of calcium in the collecting tubules is not reversible in many cases. In the ten cases of Howard and Meyer[1] eight continued to show evidences of renal damage for periods of six to eighteen months after discharge. Our patient showed all the evidences of chronic renal insufficiency two and one-half years after discontinuing the medication.

It was an interesting finding in this case that the calcium-rich viscid fluid aspirated from the mass in the right buttock had approximately the same calcium-phosphorus ratio as normal bone (2.59).[14] This finding was also noted by Freeman et al.[15] in a case with renal and metastatic calcification of the right shoulder following ingestion of ertron. Chaplin et al.[16] reported seven cases of intoxication and two of them had periarticular cysts which contained sediment with a calcium-phosphorus ratio twice that present in bone. After discontinuing the drug and administering a low calcium diet the masses disappeared in one case and decreased in size in the other.

The occurrence of massive metastatic calcifi-

cation may lead to death and at least seven such cases have been reported. Kaufman, Beck and Wiseman[17] presented a case in which the patient developed massive metastatic calcification, renal damage and death following the intake of ertron in the treatment of arthritis. The postmortem findings were calcinosis involving the joints of the extremities, sternoclavicular joints, costosternal joints, subcutaneous tissue, myocardium, lungs, pancreas, parathyroid glands and kidneys with calcium deposits in the glomerular capsules and the tubules. It still remains debatable whether these calcifications in the various tissues follow degenerative and destructive changes in the cells, as believed by Steck and his associates,[3] or whether they are due to inability of the plasma and tissue fluid to retain calcium in solution. The latter theory is supported by Ham[18] who administered vitamin D to rats and saw no changes in the cells within twenty-four hours, yet at forty-eight hours massive pathologic calcification had occurred. The two mechanisms of pathologic calcification in human tissues have also been discussed by Vaughan, Sosman and Kinney:[19] (1) Abnormally high concentrations of calcium or phosphate in the blood with precipitation of calcium phosphate in healthy tissues as seen in hyperparathyroidism and vitamin D poisoning. (2) Local tissue damage with precipitation of calcium in the presence of normal blood levels as demonstrated by the tuberculous tubule, calcium deposition in a kidney tumor and calcification in kidney tubules following mercurial poisoning. It seems that areas where there are marked changes in the pH of the media are susceptible to the deposition of calcium salt, as in the lungs where elimination of carbon dioxide leaves the tissues more alkaline, or in the gastric mucosa where the process of secreting acid contents into the stomach leaves the secretory cells alkaline, or in the renal tubules where acidification of the urine renders these cells alkaline. Also, areas such as the renal tubules and media of the arteries are favorite sites for calcification.

SUMMARY

1. A case of vitamin D poisoning following prolonged use of Nion D (activated ergosterol) is reported. In this instance the systemic and gastrointestinal symptoms usually present in this syndrome were absent but the patient presented other characteristic clinical findings, namely, irreversible impairment of renal function and metastatic calcifications.

2. The mode of action and the mechanism of intoxication with vitamin D is discussed.

3. The potential dangers of administration of large doses of vitamin D preparations is emphasized.

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REFERENCES

1. Howard, J. E. and Meyer, R. J. Intoxication with vitamin D. *J. Clin. Endocrinol.*, 8: 895–910, 1948.
2. Reed, C. I., Struck, H. C. and Steck, I. E. Vitamin D; Chemistry, Physiology, Pharmacology, Pathology, Experimental and Clinical Investigations. Chicago, 1939. Univ. Chicago Press.
3. Steck, I. E., Deutsch, H., Reed, C. I. and Struck, H. C. Further studies on intoxication with vitamin D. *Ann. Int. Med.*, 10: 951–964, 1937.
4. Albright, F. and Reifenstein, E. C. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. The Williams & Wilkins Co.
5. Bauer, W., Marble, A. and Claflin, D. Studies on the mode of action of irradiated ergosterol. I. Its effect on the calcium, phosphorus and nitrogen metabolism of normal individuals. *J. Clin. Investigation*, 11: 1–19, 1932.
6. Hess, A. F., Weinstock, M. and Rivkin, H. Source of increase in serum calcium induced by irradiated ergosterol. *Proc. Soc. Exper. Biol. & Med.*, 26: 199, 1928.
7. Hess, A. F., Weinstock, M. and Rivkin, H. A Further report on the effect of thyroparathyroidectomy on the action of irradiated ergosterol. *Proc. Soc. Exper. Biol. & Med.*, 27: 297, 1930.
8. McLean, F. C. Activated sterols in the treatment of parathyroid insufficiency. *J. A. M. A.*, 117: 609–619, 1941.
9. Vogt, J. H. and Tønsager, A. Investigations on the bone chemistry of man. (III). Experiments to determine the phosphatase, N, P and Ca in the spongy substance of the iliac crest after vitamin D_2 medication, in steatorrhea and in Cushing's syndrome. *Acta med. Scandinav.*, 135: 245–254, 1949.
10. Albright, F. and Sulkowitch, H. W. The effect of vitamin D_2 on calcium and phosphorus metabolism; studies on four patients. *J. Clin. Investigation*, 17: 305–315, 1938.
11. Harrison, H. E. and Harrison, H. C. The renal excretion of inorganic phosphate in relation to the action of vitamin D and parathyroid hormone. *J. Clin. Investigation*, 20: 47–55, 1941.
12. Ashford, C. A. The phosphorus distribution in blood and the calcium and phosphorus excretion during hypervitaminosis D. *Biochem. J.*, 24: 661, 1930.
13. McLean, C. and Lebo, L. A. Multiple calcinosis associated with hypervitaminosis D; report of a case. *South. M. J.*, 41: 389, 1948.

14. Bogert, J. and Hastings, A. B. The calcium salts of bone. *J. Biol. Chem.*, 94: 473, 1931.
15. Freeman, S., Rhoads, P. S. and Yeager, L. B. Toxic manifestations associated with prolonged ertron ingestion. *J. A. M. A.*, 130: 197–202, 1946.
16. Chaplin, H., Jr., Clark, L. D. and Ropes, M. W. Vitamin D intoxication. *Am. J. M. Sc.*, 221: 369–378, 1951.
17. Kaufman, P., Beck, R. D. and Wiseman, R. D. Vitamin D. ("Ertron") therapy in arthritis; treatment followed by massive metastatic calcification, renal damage and death. *J. A. M. A.*, 134: 688–690, 1947.
18. Ham, A. W. Mechanism of calcification in the heart and aorta in hypervitaminosis D. *Arch. Path.*, 14: 613–626, 1932.
19. Vaughan, J. H., Sosman, M. C. and Kinney, T. D. Nephrocalcinosis. *Am. J. Roentgenol.*, 58: 33, 1947.

Significance of Potassium Depletion in Poliomyelitis*

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THE pathophysiology and the clinical aspects of poliomyelitis have been exhaustively studied from the point of view of the neuromuscular disturbance but little attention has been paid to the metabolic aspects of this disease. It is our opinion that the metabolic changes in this disease must be further investigated if all of the manifestations of poliomyelitis are to be fully interpreted. The following case report is presented as an example of the significance of a metabolic disorder in severe bulbospinal poliomyelitis:

CASE REPORT

The patient, a thirteen year old white female, was well until August 9, 1950, at which time a severe chill and headache developed, followed with nausea and vomiting. Because of persistent headache and the appearance of fever she was hospitalized on the following day. On admission her temperature was 101.5°F., pulse 120, respirations 20 and blood pressure 130/80. Marked nuchal rigidity was present and the left knee jerk was hypoactive, but otherwise the neuromuscular examination was normal. The spinal fluid contained 340 cells per cu. mm. and 75 per cent polymorphonuclears; culture was negative. On the third hospital day respirations became rapid, shallow and diaphragmatic. Weakness of the extremities became apparent at this time.

The patient was transferred to an Army General Hospital on August 12, 1950. Examination revealed a well developed, well nourished, apprehensive female appearing acutely ill, in moderate respiratory distress. Her temperature was 103°F., pulse 120, respirations 30 and blood pressure 108/70. There was no motion of the intercostal muscles; respirations were diaphragmatic and irregular. The lungs and heart were normal. Neuromuscular examination revealed incomplete, generalized, asymmetric flaccid paralysis of the muscle units of all extremities, the intercostals, the flexors of the neck, and the back and abdominal muscles. Marked nuchal rigidity was present and the reflexes were asymmetric, ranging from hypoactive to absent. Cranial nerves and sensory modalities were intact.

Lumbar puncture on admission revealed an initial pressure of 420 mm. of water; the cell count was 348 per cu. mm., with 92 per cent lymphocytes; sugar was 118 mg. per cent, protein 66.5 mg. per cent and chloride 750 mg. per cent. Four hours after admission the patient was placed in a Drinker body respirator because of progressive respiratory difficulty, tachycardia and cyanosis which had not responded to oxygen alone. There was dramatic improvement after artificial respiration was begun. The patient remained febrile throughout the next four days, exhibiting marked generalized muscle weakness. She could be removed from the respirator for short intervals only, during which time cyanosis developed. Impairment of swallowing was first noted on August 16th. Much mucoid material was aspirated from the hypopharynx and increased cyanosis and apprehension became apparent. Oxygen was administered by nasal catheter with some improvement. Swallowing became progressively impaired but an adequate airway was maintained and tracheotomy avoided by repeated pharyngeal suction, Trendelenburg positioning and aspiration of the larynx and trachea through a Flagg laryngoscope. Parenteral fluids were administered and penicillin prophylaxis was instituted. Removal from the respirator could be accomplished only with the aid of artificial respiration. Slight return of swallowing was noted by August 21st, with gradual improvement thereafter. On August 25th small amounts of fluids could be swallowed and oxygen was discontinued. Soft

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foods were started four days later and slight increase of peripheral muscle function was apparent.

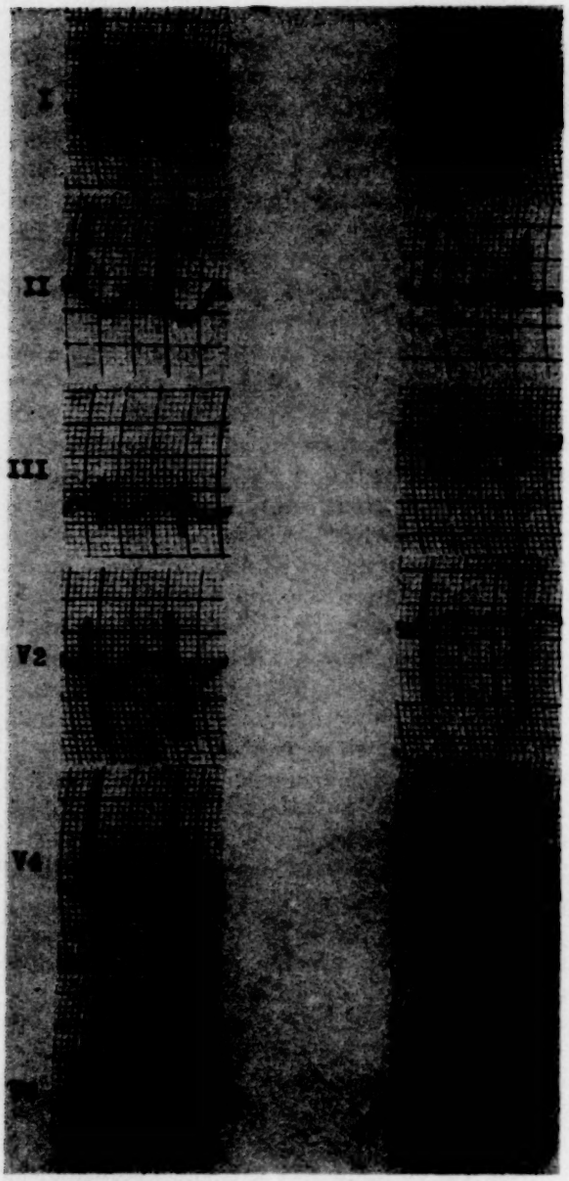
Intercostal and diaphragmatic function returned very slowly and it was not until the thirty-second hospital day that the patient could be allowed out of the respirator for short periods without supplementary positive pressure oxygen. Improvement of respiratory function was gradual but progressive so that by November 2nd use of the Drinker respirator could be discontinued. However, during this period three episodes of severe gastrointestinal disturbance were noted, occurring at approximately two-week intervals and lasting for two to three days. They were characterized by nausea, vomiting, abdominal pain, epigastric distention, weakness and lethargy. The upper abdomen was distended, tympanitic and tender, although there was no muscle spasm or rebound tenderness, and peristalsis was audible but diminished. A large amount of green gastric fluid and air was removed each time by Levin tube with marked relief. Several x-ray films of the abdomen were negative and there was no clinical evidence of mechanical intestinal obstruction. The opinion of the surgical consultant was "acute gastric dilatation." Therapy consisted of parenteral fluids and intermittent gastric aspiration. Milk formula and fruit juices were given by the Levin tube as soon as possible and some clinical improvement was observed. Oral liquids, casein hydrolysate and soft diet were resumed but the nutritional response remained inadequate. Anorexia, although previously present, now became prominent.

A fourth episode of gastric dilatation occurred on November 8, 1950, accompanied with marked lethargy. An electrocardiogram on November 9th showed S-T segment depression, flattened and inverted T waves, U waves, and a QTc* of 0.46 seconds. It was interpreted as compatible with metabolic, anoxic or myocardial changes. No previous electrocardiograms had been taken for comparison. On both November 9th and 10th 90 mEq. of potassium (as 10 per cent monobasic potassium phosphate) were administered by nasogastric tube between intermittent suction. Only slight improvement was noted clinically and the patient had to be returned to the respirator on November 11th because of weakness, fatigue, restlessness, difficult breathing and inadequate oxygenation. Serial electrocardiograms on November 9th and 10th showed no significant change. On November 12th there was only a slight increase in the voltage of the T waves in all leads although the QTc still measured 0.46 seconds. Intermittent feedings had again been accomplished by means of the Levin tube and the patient improved. On November 15th artificial respiration was discontinued, the nasogastric tube removed and oral feeding encouraged.

The fifth episode of nausea and vomiting occurred on November 25th; on the next day the patient complained of precordial pain unrelated to respiration. For the first time a harsh, poorly radiating grade 3 systolic murmur was heard at the pulmonic area. A chest x-ray on November 27th was normal; the electrocardiographic changes persisted. On November 29th the serum potassium was 3.55 mEq./L. Abdominal distention recurred on December 5th, again necessitating aspiration. An electrocardiogram on December 5th was markedly abnormal (Fig. 1), showing increased depression of the S-T segment and T wave inversions with prolongation of the QTc to 0.54 seconds. The serum potassium was 3.25 mEq./L. For the next three days 80 mEq. of potassium were given daily in the subcutaneous clysis in addition to 90 mEq. daily by Levin tube. A serum potassium on December 7th measured 3.98 mEq./L. On December 8th significant clinical and electrocardiographic improvement was noted. (Fig. 1.) The S-T segment abnormalities had disappeared, the T waves were of normal voltage and the QTc measured 0.40 seconds. The patient continued to receive approximately 90 mEq. of potassium daily by the oral route; however, on December 11th the electrocardiographic abnormalities were again noted. During the next two days an additional 120 mEq. of potassium were administered by subcutaneous clysis, the amplitude of the T waves again increased and the Q-T interval diminished. Oral monobasic potassium phosphate was continued and only minor electrocardiographic variations were noted.

Abdominal pain and nausea recurred on December 22, 1950, and gastric aspiration was

* The corrected Q-T interval (QTc) was measured according to the method of Taran and Szilagyi (1): $QTc = \frac{QT}{\sqrt{R - R'}}$ where QT equals the measured Q-T interval in seconds, and $R - R'$ equals the length of the cardiac cycle in seconds. The normal range is 0.38 to 0.42 seconds.



December 5, 1950 December 8, 1950

FIG. 1. Electrocardiograms taken before and after parenteral potassium therapy was instituted.

reinstituted. An electrocardiogram showed increased voltage of P waves, slight decrease of the voltage of T waves and change to a vertical electrical position. Eighty milliequivalents of potassium were given by subcutaneous clysis in addition to the daily oral potassium. The patient became very restless, respirations were difficult and cyanosis was apparent. She was placed in the respirator at 8:15 P.M., appearing to be in continuous abdominal pain, and expired suddenly at 2:50 A.M. on December 23, 1950.

Autopsy revealed a malnourished white female exhibiting atrophic peripheral musculature and minimal adipose tissue. The tracheobronchial tree was patent and there was no evidence of atelectasis or pneumonic consolidation. The heart was grossly normal, with no valvular or endocardial lesions. No obstructive or intrinsic lesions were found in the gastrointestinal tract and no distention was noted.

Microscopically, the central nervous system demonstrated the characteristic residuals of bulbospinal poliomyelitis. In the lungs the pulmonary alveoli were dilated and the septa were ruptured in areas. The myocardial fascicles were separated by edema in some areas but there was no evidence of leukocytic infiltration, muscle necrosis or scarring. The kidneys revealed diffuse degeneration of the lining epithelium of the collecting tubules with fibrous replacement and calcium deposition in many of these tubules. The epithelium of the convoluted tubules appeared intact although scattered foci of fibrosis and calcification were seen in this region.

COMMENTS

Although the immediate cause of death in this case is unknown, the lack of anatomic findings sufficient to explain the fatal outcome suggests a possible metabolic disturbance. Potassium intoxication can be excluded by the absence of clinical evidence of renal impairment, the lack of electrocardiographic findings of hyperkalemia, the subcutaneous route of administration of potassium and the many sources of loss of this ion.

Observed Hypokalemia in Poliomyelitis. Earle[2] reported consistently low serum potassium levels in patients with severe spinal or bulbar poliomyelitis. This finding occurred in patients who had had no vomiting or diarrhea and the potassium deficit was therefore presumed to be the result of low intake. Lans et al.[3] demonstrated potassium deficiency in six cases of bulbar poliomyelitis in which clinical and laboratory response was obtained with adequate parenteral potassium therapy.

Sources of Potassium Depletion in Poliomyelitis. Studies of renal excretion of potassium demonstrated that there is obligatory excretion of this cation and that under conditions of reduced intake a definite negative potassium balance develops.[4] Duncan[5] demonstrated that potassium losses can be very rapid and that as much as

200 mEq. may be excreted daily during periods of starvation as short as four days. Only when there is considerable potassium depletion is there any conservation by the kidneys.[6] Potassium depletion in poliomyelitis may therefore be ascribed chiefly to reduced intake due to anorexia and nausea. If there is bulbar involvement, the difficulty in swallowing aggravates the failure to maintain adequate intake; and if the physician supports the patient with potassium-free parenteral feeding, he contributes further to the growing potassium deficit. In the presence of gastrointestinal atony not only is there diminished potassium intake but there is also evidence of interference with absorption of gases, foods and fluids because the normal rhythmic contractions which aid this process are feeble or absent.[7] This phenomenon could have been the reason for the failure of response to oral potassium therapy reported by Earle[2] and observed in our case.

In severe poliomyelitis body protein loss with negative nitrogen balance results from muscle atrophy,[8] "toxic destruction of protein," namely, breakdown occurring in many febrile states,[9,10] and possibly from direct muscle cell involvement by the virus.[11] Bower et al.[12] reported that serum albumin levels fell within three to ten days after the onset of the disease—too soon to be caused by malnutrition. Potassium loss accompanies this tissue catabolism in proportion to the nitrogen loss, namely, 2.4 mEq. of potassium per gm. of nitrogen lost,[13] although there is evidence that potassium administration may disturb this parallelism.[14] The intracellular potassium reserve becomes smaller in proportion to the circulating ion and there is loss of the "buffering effect" of the intracellular mass so that serum levels become less stable and more responsive to outside influences.

In acute conditions associated with stress phenomena there is shift of potassium from the intracellular to the extracellular space.[15–17] Much of the potassium so liberated is lost, either by direct urinary excretion or by transfer to the liver, with later elimination through the kidney.[18,19] It is probable that a portion of the potassium lost in acute poliomyelitis can be accounted for in this process. Although protracted vomiting is not common in poliomyelitis, when it does occur it becomes a significant source of potassium loss. The development of cellular potassium deficit is rapid and profound,[20] for not only is there loss of large quantities of potassium in the vomitus with development of hypochloremic alkalosis[21,22] but also the resulting alkalosis itself leads to excessive urinary potassium excretion.[23,24]

Gastrointestinal Disturbances in Poliomyelitis. Anorexia, nausea, vomiting, constipation and transient pain of gastrointestinal origin are common in poliomyelitis.[25] These are observed most often in the second stage of poliomyelitis and occasionally may obscure the nervous symptoms.[26] Later, during the course of the bulbar or bulbospinal types, these manifestations may be observed again. Schönholzer[27] reported an instance of complete gastrointestinal tract paralysis without evidence of obstruction at autopsy. A similar case showing marked gastric atony and dilatation was described by Waltz[28] who, citing the work of several other authors, stated that "this observation has been made very often." It is believed that reflex disturbances may lead to the development of those gastrointestinal manifestations which are seen early in the course of the disease; however, the etiology of the more severe changes seen later, such as in our case and in those of Schönholzer and Waltz, is more obscure.

Gastrointestinal signs similar to those described heretofore are seen in potassium depletion states. Experimentally, changes varying from inhibition of intestinal musculature[7,29] to fatal paralytic ileus[30] have been produced by creating potassium deficiency in laboratory animals. Clinically, nausea, vomiting, abdominal distention and ileus have been observed in association with intracellular deficiency of this ion.[13,31–33] In severe poliomyelitis the intestinal atony may be due to the direct effect of potassium lack and contributes significantly to progressive total body potassium depletion. (Fig. 2.)

Muscular Disturbance in Potassium Depletion. Muscle involvement represents one of the most prominent clinical manifestations of potassium deficiency states. Skeletal muscle disturbances may vary from simple weakness to flaccid paralysis of the extremities and the respiratory musculature which, if untreated, may lead to respiratory paralysis and death.[34,35] Lans[3] commented on the inability of the patient with bulbar poliomyelitis to tolerate such an additional burden on respiratory function.

Effects of Potassium Deficiency on the Cardiovascular System. The principal electrocardiographic abnormalities referable to low concentration of

serum potassium are diminished amplitude and inversion of the T waves, prolongation of the Q-T interval and depression of the S-T segment. U waves are often present.[13,36–39] These changes have been found after excessive loss of intestinal contents and in the postoperative state,[40] as well by their occurrence almost four months after the onset of poliomyelitis and their failure to disappear after the patient had been returned to the respirator with consequent improvement of tidal exchange and oxygenation. Furthermore, the reversal of these changes to normal after

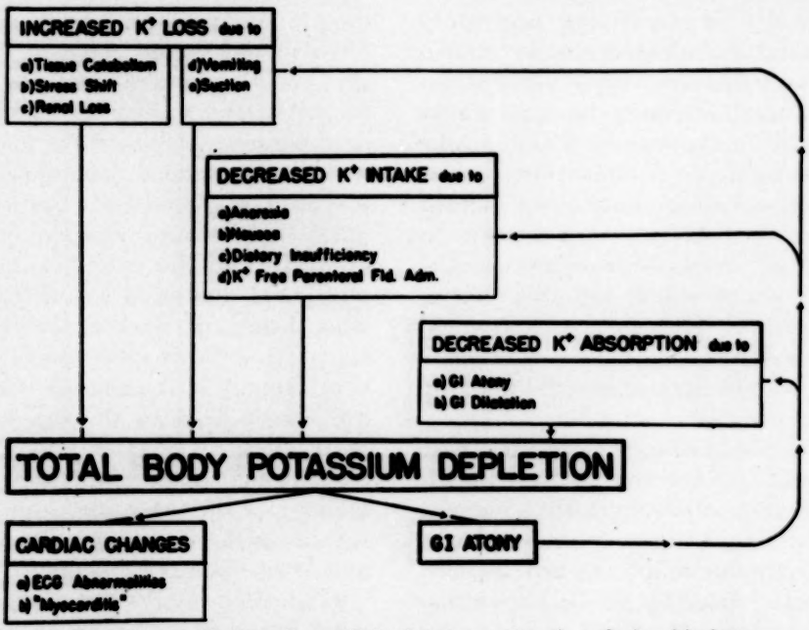


FIG. 2. Potassium cycle in poliomyelitis, demonstrating the relationship between the causes and effects of potassium depletion.

as in chronic nephritis,[39] familial periodic paralysis[41] and recovery from diabetic acidosis.[37,42] Eliel et al.[40] discussed several postoperative patients known to have had potassium deficiency on the basis of balance studies. They demonstrated lowered amplitude of T waves coincident with the development of alkalosis and hypochloremia, which preceded a fall in serum potassium levels. They suggested that the electrocardiogram may in some instances be a better index of tissue potassium deficit than of the serum level. These findings are consistent with the observation that there may be a considerable tissue potassium deficit without marked reduction of the circulating level[4,32] as encountered in our patient and as observed by Earle[2] and Lans.[3] It must be appreciated that the electrocardiogram is not properly a substitute for the laboratory measurement of the serum potassium but is an important adjunct in diagnosis if serial tracings are obtained.[36,43] The non-specific electrocardiographic abnormalities observed in our case were not due to infectious myocarditis or to anoxia, as evidenced potassium therapy is at least confirmatory if not pathognomonic evidence of their correlation with a state of potassium depletion.

It is of interest that the effect of potassium deficiency on the heart is not only one of electrocardiographic changes. Bellet[36] commented on the occurrence of systolic murmurs in hypokalemia; in addition, pathologic changes have been noted both in experimental animals and man. Microscopic cardiac changes have been encountered in a case of chronic diarrhea with potassium depletion[44] and in a patient with treated Addison's disease in whom a potassium deficit occurred.[45] Other observers[46–49] have reported microscopic and gross cardiac lesions in rats which had been fed diets deficient only in potassium. Follis et al.[46] described microscopic changes as early as the eighth day consisting of loss of striation of individual muscle fibers followed with nuclear shrinking and destruction. There were associated areas of muscle necrosis accompanied with leukocytic infiltration, at first with polymorphonuclear and later with mononuclear phagocytes

predominating. Within fifteen days the lesions became large and numerous, and in some animals the process took on the appearance of diffuse myocarditis with areas suggesting the lesions of human diphtheria. Necrotic areas continued to appear as long as the animals were on a diet deficient in potassium; however, coexistent healing by proliferation of connective tissue and scarring was observed in the earlier lesions. There was neither perivascular accumulation of leukocytes nor changes in the vessels themselves. Gross changes were seen after the third week and consisted of tiny, opaque, subepicardial, gray necrotic areas. In comparison with the controls there seemed to be evidence of cardiac hypertrophy in the potassium-deficient animals. Chemically, the potassium content of the heart muscle was 35 per cent lower than that of the controls. In addition, microscopic examination of the kidneys in the deficient animals revealed necrosis of the tubular epithelium of the convoluted tubules and deposition of "calcified material" in the lumina of some of the tubules.

Myocardial and electrocardiographic changes are not uncommon in poliomyelitis. Although previous reports had appeared in the literature,[50–52] Saphir and Wile[53] in 1942 first focused attention on myocarditis in poliomyelitis, demonstrating changes in six of seven autopsied patients. Findings of similar myocardial changes have been noted by many authors since then.[54–59] Spain et al.[58] described myocardial changes in twelve of fourteen necropsied cases of poliomyelitis. These abnormalities consisted of interstitial edema, diffuse, focal and perivascular leukocytic infiltration, focal myocardial necrosis and fibroblastic proliferation. Electrocardiographic changes, consisting mainly of prolongation of the Q-T interval, have been reported by Joos and Yu[60] in five of twenty-three cases. Bradford and Anderson[61] noted abnormalities of the S-T segment and T waves in 12 per cent of 155 patients with poliomyelitis and in four of five fatal cases. Electrocardiographic changes were described in a single case of fatal bulbospinal poliomyelitis by Boucek and his associates;[62] at autopsy edema, cellular infiltration and necrotizing focal lesions were found in the myocardium.

The pathologic cardiac findings in poliomyelitis are striking in their similarity to potassium deficiency "myocarditis"; only perivascular infiltration was lacking in the latter. Furthermore, the myocarditis in poliomyelitis is nonspecific and cannot be differentiated from that seen in other infectious diseases.[63] The etiology of this myocarditis has been attributed to viral origin "by the failure clinically to find any other satisfactory explanation and also by the production of similar lesions with human virus in suitable experimental animals, as well as by the demonstration of the virus in the human myocardium."[64] The virus was demonstrated in three of five human cases, in only one of which extensive myocarditis was present. Since the virus has also been isolated from skeletal muscle and blood, its recovery from the heart does not establish *a priori* evidence that the virus causes the myocardial damage. From a purely speculative standpoint, it would be worth considering the possibility that the changes in the myocardium which occur in poliomyelitis may be due in part to a metabolic cause, at least in the more severe cases in which potassium deficiency exists. This concept, we believe, is worthy of closer clinical and pathologic investigation and correlation.

SUMMARY AND CONCLUSIONS

1. The case presented demonstrates the significance of potassium depletion in severe bulbospinal poliomyelitis.

2. It is suggested that the myocardial and electrocardiographic changes which have been observed in poliomyelitis have a metabolic component.

3. The use of serial electrocardiograms proved valuable in the detection and management of potassium deficiency and is recommended when the clinical course suggests a metabolic disturbance in this disease.

4. In our opinion the observed episodes of gastrointestinal atony and dilatation, nausea and vomiting were due to potassium deficiency and contributed significantly to continued potassium loss, thereby establishing a self-perpetuating cycle.

5. Potassium depletion of large magnitude is inherent in this cycle; hence therapy must be directed toward replenishing the total body stores, not at temporarily restoring serum potassium levels or reversing electrocardiographic changes.

6. It is our opinion that potassium deficiency must be considered in the management of any patient seriously ill with poliomyelitis.

REFERENCES

1. Taran, L. M. and Szilagyi, N. The duration of the electrical systole (Q-T) in acute rheumatic carditis in children. *Am. Heart J.*, 33: 14, 1947.
2. Earle, A. M. Serum potassium in poliomyelitis. *J. Pediat.*, 36: 715, 1950.
3. Lans, H. S., Stein, I. F., Becker, R. J., Hoyne, A. L. and Meyer, K. A. Potassium deficiency in bulbar poliomyelitis. *J. A. M. A.*, 146: 1017, 1951.
4. Tarail, R. and Elkinton, J. R. Potassium deficiency and the role of the kidney in its production. *J. Clin. Investigation*, 28: 99, 1949.
5. Duncan, L. E., Meyer, R. J. and Howard, J. E. Mineral balance during brief starvation. The effect on serum electrolytes and mineral balance of maintaining the intake of certain mineral constituents. *J. Clin. Investigation*, 27: 389, 1948.
6. Martin, H. E. Clinical potassium problems. *California Med.*, 72: 133, 1950.
7. Hendrikson, H. W. Effect of potassium deficiency on gastrointestinal motility in rats. *Am. J. Physiol.*, 164: 263, 1951.
8. Peters, J. P. and Van Slyke, D. D. Quantitative Clinical Chemistry, pp. 648–656. Baltimore, 1931. Williams & Wilkins Co.
9. Grossman, C. M. Nitrogen metabolism in acute infections. *J. Clin. Investigation*, 24: 523, 1945.
10. Peters, J. P. Problems of nitrogen metabolism. *Federation Proc.*, 3: 197, 1944.
11. Denst, J. and Neuberger, K. T. A histologic study of muscles and nerves in poliomyelitis. *Am. J. Path.*, 26: 863, 1950.
12. Bower, A. G., Eaton, R. M., Chudnoff, J. S., Affeldt, J. E. and Chaney, A. L. Patterns of plasma protein changes in acute poliomyelitis patients: treatment with blood plasma. *Am. J. M. Sc.*, 220: 46, 1950.
13. Hoffman, W. S. Clinical physiology of potassium. *J. A. M. A.*, 144: 1157, 1950.
14. The movement of potassium during the protein catabolic reaction after trauma. Conference on the Metabolic Aspects of Convalescence, Tenth Meeting, pp. 272–302, 1945.
15. Fox, C. L., Jr. and Baer, H. Redistribution of potassium, sodium and water in burns and trauma, and its relation to phenomena of shock. *Am. J. Physiol.*, 151: 155, 1947.
16. Hoaglund, H. and Stone, D. Brain and muscle potassium in relation to stressful activities and adrenal cortex function. *Am. J. Physiol.*, 152: 423, 1948.
17. Selye, H. The Physiology and Pathology of Exposure to Stress, pp. 196–199. Montreal, Canada, 1950. Acta, Inc.
18. Fenn, W. O. Fate of potassium liberated from muscles during activity. *Am. J. Physiol.*, 127: 356, 1939.
19. Fenn, W. O. The role of potassium in physiological processes. *Physiol. Rev.*, 20: 377, 1940.
20. Mudge, G. H. and Vislocky, K. Electrolyte changes in human striated muscle in acidosis and alkalosis. *J. Clin. Investigation*, 28: 482, 1949.
21. Gamble, J. L. and Ross, S. G. The factors in the dehydration following pyloric obstruction. *J. Clin. Investigation*, 1: 403, 1925.
22. Kennedy, T. J., Jr., Winkley, J. H. and Dunning, M. H. Gastric alkalosis with hypokalemia. *Am. J. Med.*, 6: 790, 1949.
23. Burnett, C. H., Burrows, B. A. and Commons, R. R. Studies of alkalosis, I; renal function during and following alkalosis resulting from pyloric obstruction. *J. Clin. Investigation*, 29: 169, 1950.
24. Burnett, C. H., Burrows, B. A., Commons, R. R. and Towery, B. T. Studies of alkalosis, II; electrolyte abnormalities in alkalosis resulting from pyloric obstruction. *J. Clin. Investigation*, 29: 175, 1950.
25. Grulee, C. G. and Panos, T. C. Epidemic poliomyelitis in children. *Am. J. Dis. Child.*, 75: 24, 1948.
26. Holt, L. E., Jr. and McIntosh, R. Holt's Diseases of Infancy and Childhood, 11th ed., pp. 1172–1181. New York, 1940. D. Appleton-Century Co.
27. Schönholzer, G. Über Störung der vegatativen Innervation bei der Poliomyelitis anterior acuta. *Deutsches Arch. f. klin. Med.*, 180: 394, 1937.
28. Waltz, W. Akute Magendilatation bei Heine-Medin'scher Krankheit. *Berl. klin. Wchnschr.*, 58: 667, 1921.
29. Webster, D. R., Hendrikson, H. W. and Currie, D. J. The effect of potassium deficiency on intestinal motility and gastric secretion. *Ann. Surg.*, 132: 779, 1950.
30. Winter, H. A., Hoff, H. E. and Dso, L. Effect of potassium deficiency upon gastrointestinal motility. *Federation Proc.*, 8: 169, 1949.
31. Randall, H. T., Habif, D. V., Lockwood, J. S. and Werner, S. C. Potassium deficiency in surgical patients. *Surgery*, 26: 341, 1949.
32. Danowski, T. S. Newer concepts of the role of potassium in disease. *Am. J. Med.*, 7: 525, 1949.
33. Darrow, D. C. Body-fluid physiology: the role of potassium in clinical disturbance of body water and electrolytes. *New England J. Med.*, 242: 978 and 1014, 1950.
34. Darrow, D. C. and Pratt, E. L. Fluid therapy relation to tissue composition and the expenditure of water and electrolyte. *J. A. M. A.*, 143: 365 and 432, 1950.
35. Bodansky, O. Recent advances in parenteral fluid therapy with ammonium chloride and potassium. *Am. J. M. Sc.*, 218: 567, 1949.
36. Bellet, S., Steiger, W. A., Nadler, C. S. and Gazes, P. C. Electrocardiographic patterns in hypopotassemia: observations on 79 patients. *Am. J. M. Sc.*, 219: 542, 1950.
37. Nadler, C. S., Bellet, S. and Lanning, M. Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. *Am. J. Med.*, 5: 838, 1948.
38. Bellet, S., Nadler, C. S., Gazes, P. C. and Lanning, M. Effect of vomiting due to intestinal obstruction on the serum potassium. *Am. J. Med.*, 6: 712, 1949.
39. Brown, M. R., Currens, J. H. and Marchand, J. F. Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. *J. A. M. A.*, 124: 545, 1944.
40. Eliel, L. P., Pearson, O. H. and Rawson, R. W. Postoperative potassium deficit and metabolic alkalosis. *New England J. Med.*, 243: 471, 1950.

41. Stewart, H. J., Smith, J. J. and Milhorat, A. T. Electrocardiographic and serum potassium changes in familial periodic paralysis. *Am. J. M. Sc.*, 199: 789, 1940.
42. Holler, J. W. Potassium deficiency occurring during treatment of diabetic acidosis. *J. A. M. A.*, 131: 1186, 1946.
43. Tarail, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.*, 5: 828, 1948.
44. Perkins, J. G., Petersen, A. B. and Riley, J. A. Renal and cardiac lesions in potassium deficiency due to chronic diarrhea. *Am. J. Med.*, 8: 115, 1950.
45. Goodof, I. J. and MacBryde, C. M. Heart failure in Addison's disease with myocardial changes of potassium deficiency. *J. Clin. Endocrinol.*, 4: 30, 1944.
46. Follis, R. H., Orent-Keiles, E. and McCollum, E. V. The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. *Am. J. Path.*, 18: 29, 1942.
47. Schrader, G. A., Prickett, C. O. and Salmon, W. D. Symptomatology and pathology of potassium and magnesium deficiencies in the rat. *J. Nutrition*, 14: 85, 1937.
48. Thomas, R. M., Mylon, E. and Winternitz, M. C. Myocardial lesions resulting from dietary deficiency. *Yale J. Biol. & Med.*, 12: 345, 1940.
49. Darrow, D. C. and Miller, H. C. Production of cardiac lesions by repeated injections of desoxycorticosterone acetate. *J. Clin. Investigation*, 21: 601, 1942.
50. Robertson, H. E. and Chesley, A. J. Pathology and bacteriology of anterior poliomyelitis. *Arch. Int. Med.*, 6: 233, 1910.
51. Abramson, H. L. Pathologic report on 43 cases of acute poliomyelitis. *Arch. Int. Med.*, 22: 312, 1918.
52. Cowie, D. M., Parsons, J. P. and Lowenberg, K. Clinico-pathologic observations on infantile paralysis. *Ann. Int. Med.*, 8: 521, 1934.
53. Saphir, O. and Wile, S. A. Myocarditis in poliomyelitis. *Am. J. M. Sc.*, 203: 781, 1942.
54. Peale, A. R. and Lucchesi, P. F. Cardiac muscle in poliomyelitis. *Am. J. Dis. Child.*, 65: 733, 1943.
55. Saphir, O. Visceral lesions in poliomyelitis. *Am. J. Path.*, 21: 99, 1945.
56. Dolgopol, V. B. and Cragan, M. D. Myocardial changes in poliomyelitis. *Arch. Path.*, 46: 202, 1946.
57. Ludden, T. E. and Edwards, J. E. Carditis in poliomyelitis; an anatomic study of 35 cases and review of the literature. *Am. J. Path.*, 25: 357, 1949.
58. Spain, D. M., Bradess, V. A. and Parsonnet, V. Myocarditis in poliomyelitis. *Am. Heart J.*, 40: 336, 1950.
59. Weinstein, L. and Shelokov, A. Cardiovascular manifestations in acute poliomyelitis. *New England J. Med.*, 244: 281, 1951.
60. Joos, H. A. and Yu, P. N. G. Electrocardiographic observations on poliomyelitis. *Am. J. Dis. Child.*, 80: 22, 1950.
61. Bradford, H. A. and Anderson, L. L. Electrocardiographic observations during a poliomyelitis epidemic. *Ann. Int. Med.*, 32: 270, 1950.
62. Boucek, R. J., Bailey, A. A., Burchell, H. B. and Edwards, J. E. Cardiac Clinics cxxx. Myocardial disease in acute poliomyelitis. *Proc. Staff Meet., Mayo Clin.*, 24: 495, 1949.
63. Appel, M. Poliomyelitis, a clinical pathological correlation. *Illinois M. J.*, 98: 190, 1950.
64. Editorial. Myocarditis in poliomyelitis and related viral infections. *Ann. Int. Med.*, 34: 1502, 1951.

Morphology of Healed Tuberculous Meningitis Following Streptomycin Therapy

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ALTHOUGH numerous cases of tuberculous meningitis clinically healed after streptomycin therapy have appeared in the recent literature, a careful review fails to disclose autopsy studies of completely resolved disease. Various stages of response to therapy, interrupted by death, have been subjected to histologic and gross examination but no description of the pathologic findings after complete recovery, clinical and anatomic, could be found. The purpose of this paper is to place on record an example of such a case, with subsequent death due to adrenal insufficiency.

Feldman, Hinshaw and Mann,[1] using streptomycin in experimental tuberculosis, concluded that "although capable of striking deterrent effects in combating or preventing anatomic changes due to Mycobacterium tuberculosis, streptomycin in most instances exerted a suppressing rather than a sterilizing effect on the effecting agent." Of the twelve patients with miliary tuberculosis with meningitis, later treated by them,[2] nine had clinical evidence of focal cerebral lesions of tuberculosis and in two these were demonstrated at necropsy. Later, Baggenstoss et al.[3] found that after streptomycin therapy tuberculosis lesions may heal in some organs while active progression occurred in others; and that although no evidence of meningitis could be found on the surface of the brain or spinal cord, widespread lesions were found in the brain proper. They postulated "a so-called pia-glial barrier" which prevents streptomycin from reaching the brain.

Bunn[4] believed that as a result of the gross and microscopic findings in eight of sixteen patients who died of tuberculous meningitis while undergoing streptomycin therapy the antibiotic had no effect on the progression of disease. All of these patients had similar findings at autopsy: active arachnoiditis; thick fibrinous exudate over the pons and medulla; epithelioid tubercles; infarcts due to thrombosis and tubercles in the brain substance. In its contemporary report the Council on Pharmacy and Chemistry of the American Medical Association[5] stated that "pathologic studies which are now in progress should add considerably to existing knowledge of the pathologic changes and pathogenesis of both pulmonary and meningeal lesions." Two years later it reported[6] that "pathologic studies of the brains of patients who died with tuberculous meningitis disclosed destruction of the basal ganglia in 23 %, healing by fibrosis in 45 per cent and some degree of hydrocephalus in 75 %."

Tagliaferro,[7] Berblinger[8] and Ascenzi and Benedetti[9] all agreed with Bunn[4,10] that streptomycin is bacteriostatic but will not prevent dissemination of the bacilli. Anatomic studies by Pana[11] revealed recent and older tubercles and amorphous or partially organized exudate of non-specific character. The development of miliary tubercles was arrested outside of the nervous system, occasionally they were completely fibrosed. Tackett and Lovejoy[12] came to essentially similar conclusions after following a case for twenty-seven months with death from reactivation of meningeal tuberculosis. Likewise, Pero and Reimann[13] and Netsky, Ritter and Zimmerman[14] failed to find complete resolution in numerous autopsied cases. Acquilina,[15] however, reported a patient with clinically cured tuberculous meningitis who was alive three years following the onset and well except for residuals of left eye blindness and slight weakness of the left leg.

CASE REPORT

A white, married, thirty-two year old railroad laborer was first seen by one of the authors (S. M. J.) on November 24, 1943. He complained of interscapular pain for over a year. X-rays revealed a fusiform mass in the posterior mediastinum. The lungs were clear. Cardiac

chamber visualization was incomplete. The mass was considered to be an aneurysm of the descending aorta. The blood pressure was 110/60, serologic tests for syphilis were negative and the spinal fluid was normal.

In January, 1944, the patient was inducted into the U.S. Navy. In March, 1944, he was hospitalized following an "injury." The medical staff concurred at first in the diagnosis of aortic aneurysm but the final diagnosis was "tuberculous arthritis" involving the eighth and ninth dorsal vertebrae. There was now prominence of these dorsal vertebrae and the mass was considered to be a cold abscess. A PPD test was positive 1 plus, first strength; chest x-ray showed generalized miliary tuberculosis and repeated smears and cultures of the sputum were negative. He was discharged in May, 1944.

On January 11, 1947, he was seen by one of us (S. M. J.) complaining of headache of three weeks' duration. The temperature was 100.5°F., pulse 99, respiration 20. The next morning, after admission to the Memorial Hospital in Cumberland, Maryland, the temperature was 103.6°F., pulse 100. He was comatose, irrational, had moderate neck rigidity, bilateral Kernig's signs and a Brudzinski sign. Red blood count 4,360,000, hemoglobin 84 per cent, white blood count 8,200, polymorphonuclears 68, lymphocytes 27, eosinophils 5. Urinalysis revealed 10 mg. albumin and a few white and red blood cells. The spinal fluid was clear, Queckenstedt's sign negative, cells 244, lymphocytes 70 per cent. No pedicle formed after twenty-four hours and the smear was negative. However, the culture was positive for tuberculosis. X-rays of the dorsal spine revealed marked destruction of the body of the ninth dorsal vertebra. The lungs were "essentially clear."

Streptomycin in divided doses, 3 gm. intramuscularly and 0.2 gm. intrathecally, was administered daily for eighteen days. Then the dosage was gradually decreased until a total of 244.5 gm. was reached. On January 20th he was completely rational. On February 14th his temperature was 102°F., spinal fluid cell count 363 and he became delirious. On February 25th his temperature was 105°F., cell count 309, pulse rate rapid, tongue dry, neck rigid. He was irrational, unable to void, uncooperative and required an inlying catheter, intravenous glucose, protein, and vitamin supplements and sedation. However, by February 28th he was improved and rational with subsidence of all

FIG. 1. Enlargement of right ventricle.

symptoms. On June 20th the spinal fluid was clear, containing 72 lymphocytes per cu. mm. Complete blood count and urinalysis were normal. He was completely deaf (however, there was a history of right ear deafness since childhood). On June 23, 1947, he was discharged.

On August 12, 1947, January 6, 1948, March 22, 1949, and March 2, 1950, and February 26, 1951, spinal fluid examinations were all negative, including cultures and guinea pig inoculations. However, he complained of weakness, giddiness, deafness and headaches. He learned lip reading, sired two children and helped to build a small house for his family. At this point his case was included in Bunn's report.[4]

On April 18, 1951, symptoms of swelling of the feet, choking, dyspnea and orthopnea ensued. Examination revealed pitting edema of feet and ankles, cyanosis, and 2 plus fulness of the neck veins. The liver was felt five fingerbreadths below the costal margin. There was protrusion of the sixth, seventh and eighth thoracic vertebrae and distant breath sounds at both bases. The pulse was 96 and the blood pressure (in the right arm) 86/52. Fluoroscopy revealed a large globular heart. Electrocardiogram showed sinus tachycardia, right axis deviation and evidence of coronary and myocardial disease.

He was admitted to the Newton D. Baker Veterans Administration Hospital in Martinsburg, West Virginia, on April 21, 1951. Physical examination revealed a "dusky" skin; cyanosis of the lips, conjunctivae and finger tips; distended neck veins and moderate kyphosis. There were numerous moist inspiratory rales. The maximal cardiac impulse was over the xiphoid process, pulse rate 102 per minute and regular.

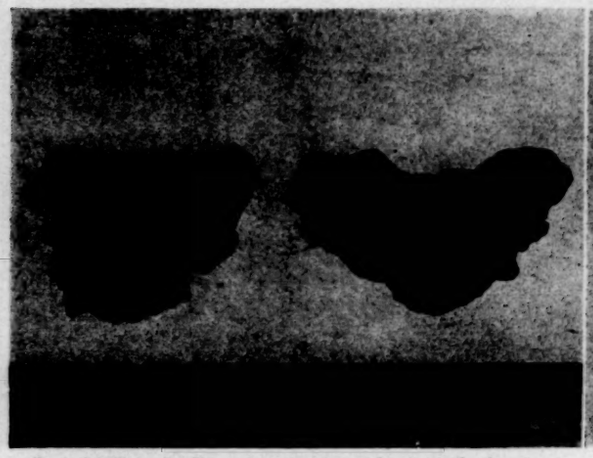

FIG. 2. Tuberculous destruction of adrenal glands.

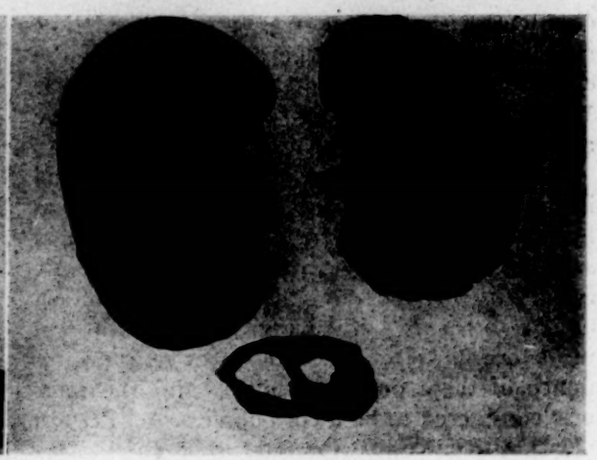

FIG. 3. Renal cavitation.

The first sound over the xiphoid was accentuated and was accompanied by a presystolic and a diastolic murmur. The blood pressure was 108/70, there was two plus pitting edema of the feet and ankles, the venous pressure was 28 cm. (water). The liver was palpable three finger-breadths below the right costal margin and not tender.

Admission fluoroscopy revealed an increase in the hilar shadows, straightening of the left cardiac silhouette, enlargement of the pulmonary artery and a small aortic knob.

The admission red blood count was 4,850,000, hemoglobin 15 gm., hematocrit 48 per cent, white blood and differential counts were normal. The urine showed a trace of albumin. The serologic tests for syphilis in blood and spinal fluid were normal. There was no growth on culture of the spinal fluid. The fasting eosinophile count was 22, carbon dioxide combining power 45 vol. per cent, serum NPN 35 mg. per cent. The serum potassium was 5.6 mEq./L. Electrocardiograms suggested right ventricular hypertrophy. X-rays showed an enlarged cardiac silhouette with straightening of the pulmonic segment of the left auricle, increased hilar and pulmonic markings, irregularity of the eighth dorsal vertebrae and destruction of the body of the ninth dorsal vertebrae with marked spinal angulation.

The patient was comfortable on admission and afebrile until death at which time his temperature was 100.6°F. rectally. Respirations varied from 30 to 50 per minute, pulse between 80 to 110. He was put to bed rest and given a salt-free diet, digitalis and mercurial diuretics. On this therapy he lost 10 pounds in a week. On April 26, 1951, after the insertion of a gastric tube for analysis, he was given 0.5 cc. of $\frac{1}{1000}$ histamine phosphate subcutaneously. In ten minutes he became markedly cyanotic and dyspneic and developed pulmonary edema. He was promptly given oxygen by mask at the rate of 12 L. per minute and within five minutes the color of his skin was nearer normal than at any time since admission. Three minim of adrenalin chloride were given subcutaneously. His pulmonary edema cleared, although anorexia, nausea and vomiting continued. Forty mEq. of potassium chloride in 1,000 cc. of 5 per cent glucose were given on May 4th although he had no electrocardiographic evidence of hypopotassemia. At this time it was noted that the right knee jerk and the Achilles reflex were absent. He became stuporous, dyspneic and died in one-half hour.

The positive gross findings at autopsy were: marked dorsal kyphosis; adhesion of left visceral to the parietal pleura by dense adhesions which could be separated only with difficulty; dense firm lungs from whose cut surface abundant pink frothy fluid exuded; numerous flat sclerotic placques in both pulmonary arteries whose main branches were widened. The heart weighed 350 gm. and was enlarged on the right side. (Fig. 1.) The right ventricular wall was 1 cm. thick, the left ventricular wall 1.2 cm. and the interventricular septum 1.5 cm. The capacity of the right ventricle was greater than the left ventricle. The foramen ovale was patent, 1.2 cm. long; this, however, was a mere slit and there appeared to be a flap valve "guarded" effect of its original edge. The adrenals together weighed 35 gm., the right being larger than the

left but not markedly so. (Fig. 2.) They were irregular, nodular and firm on cut section which revealed a yellowish-grey caseous process replacing all cortical and medullary tissue. Each kidney weighed approximately 150 gm. and was slightly increased in width. (Fig. 3.) On cut surface each contained a multiloculated cavity, lined by several millimeters of yellowish-grey necrotic material, well walled off from the surrounding kidney tissue and not communicating with the pelvis. The leptomeninges were not thickened except for a small area in the interpeduncular region. There was no fluid or exudate. Numerous cross sections through the brain failed to reveal gross abnormalities.

Microscopic examination revealed that in all areas of the lungs the vessels of the septi were congested and dilated and there was variable fibrosis. The arterioles and smaller arteries displayed intimal proliferation, hyaline degeneration and medial thickening. There were areas of peribronchial fibrosis with lymphocytic and polynuclear infiltration and collections of jet black anthracotic pigment. In scattered regions the alveoli contained reticuloendothial cells engulfing large brownish granules. The adrenal glands for the most part were destroyed and replaced by eosinophilic caseation necrosis but sparse "ghost-like" remnants of cortical cells appeared at the periphery just outside a zone of plasma cells, lymphocytes, fibroblasts and epithelioid cells. The walls of the renal cavitations were composed of a superficial layer of amorphous necrosis, fibrous tissue, and an outside zone of lymphocytes, plasma cells and histiocytes with many new capillaries growing in. The surrounding renal tissue displayed interstitial fibrosis with varying degrees of tubular and glomerular degeneration and many hyaline casts.

The skin of the thorax had flattened rete pegs and numerous brown granules were located perinuclearly in the basal cells. There were no chromatophores within the corium. The cerebral arachnoid was thickened and reduplicated and there was increased vascularity and fibrosis in the subarachnoid space. (Fig. 4.) The underlying Virchow-Robin spaces were widened. The ganglion cells were well preserved with no significant evidence of neuronal destruction. This quiescent process was most evident over the base and barely visible over the vertex. There were no signs of activity.

FIG. 4. Arachnoidal thickening and fibrosis over cerebral cortex.

COMMENT AND SUMMARY

The literature concerning the treatment of tuberculous meningitis with streptomycin is briefly reviewed. No case of complete cure with follow-up necropsy (after death from other cause) could be found. Such a case with residua only of scarring and without evidence of activity is presented.

REFERENCES

1. FELDMAN, W. H., HINSHAW, H. C. and MANN, F. C. Streptomycin in experimental tuberculosis. *Am. Rev. Tuberc.*, 52: 269–298, 1945.
2. HINSHAW, H. C., FELDMAN, W. H. and PFUETZE, K. H. Treatment of tuberculosis with streptomycin: a summary of observations on one hundred cases. *J. A. M. A.*, 132: 778–782, 1946.
3. BAGGENSTOSS, A. H., FELDMAN, W. H. and HINSHAW, H. C. Streptomycin in military tuberculosis: its effect on the pathological lesions of generalized miliary tuberculosis in human beings. *Am. Rev. Tuberc.*, 55: 54–76, 1947.
4. BUNN, P. A. One hundred cases of miliary and meningeal tuberculosis treated with streptomycin. *Am. J. M. Sc.*, 216: 286–315, 1948.
5. Report to the Council. Streptomycin in the treatment of tuberculosis. *J. A. M. A.*, 138: 584–593, 1948.
6. Report of the Council. Current status of the chemotherapy of tuberculosis in man. *J. A. M. A.*, 142: 650–653, 1950.
7. TAGLIAFERRO, E., FERRAI, G. and KONECNY, A. La cura streptomicinica nella meningite tubercolare (Studio clinico ed anatomoistologico). *Rass. giul. med.*, 5/5: 159–171, 1949.
8. BERBLINGER, W. Das morphologische Bild der chronischen miliären Lungentuberkulose und der Tuberkulose der Meningen nach Streptomycintherapie. *Beitr. z. Klin. Tuberk.*, 101: 611–636, 1949.
9. ASCENZI, A. and BENEDETTI, E. L. Contributo allo studio del cicio evolutivo della leptomeningite

tubercolare medificato dal trattamento con streptomicina. Sul significato istopatogenetico di alcuni rilievi istologici. *Pediat. internaz.*, 2: 37–104, 1949.

10. Bunn, P. A. Two-year follow up report of patients with miliary and meningeal tuberculosis treated with streptomycin. *Am. J. M. Sc.*, 219: 127–132, 1950.
11. Pana, C. Alcuni reperti anatomici da streptomicina. *Lotta C. Tuberc.*, 19: 311–312, 1949.
12. Tacket, H. S. and Lovejoy, S. Prolonged survival following streptomycin therapy of tuberculous meningitis. *J. A. M. A.*, 142: 648–649, 1950.
13. Pero, C. I. Meningitis tuberculosa und Streptomycin. *Deutsche Ztschr. f. Nervenheilk.*, 164: 321–331, 1950.
14. Netsky, M. G., Ritter, N. S. and Zimmerman, H. M. The effect of streptomycin on tuberculous meningitis: a study of three cases at necropsy. *Am. Rev. Tuberc.*, 62: 568–593, 1950.
15. Acquilina, J. T. Tuberculosis meningitis cured with streptomycin. *J. A. M. A.*, 147: 560, 1951.

Peripheral Neuritis from Tetanus Antitoxin*

Report of a Case Treated with Cortisone and ACTH

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PERIPHERAL neuritis is, fortunately, a rare manifestation of serum sickness. Since the most frequently administered form of horse serum is prophylactic tetanus antitoxin, this is the most frequent cause of serum neuritis. However, the disease has been reported[1] after the administration of other types of horse sera, including diphtheria and scarlet fever antitoxins and antipneumococcic and antimeningococcic sera. According to Bennett[2] neurologic complications of serum sickness were first reported in France by Gardére and Gandolphe in 1908. Most of the early cases were reported from France, and Bennett states that there were seventy cases in the French literature by 1938. The first report from the United States was that of Richardson[3] whose patient developed multiple neuritis after large doses of tetanus antitoxin given for the treatment of severe tetanus. Another early American report was Wilson and Hadden's[4] of six cases, four from tetanus antitoxin and two from diphtheria antitoxin. Doyle[1] reported two cases in 1933, one due to scarlet fever antitoxin and one due to tetanus antitoxin. Bennett's 1939 report[2] included five cases that he had seen in a six-year period. Recent reports include those of Comroe and coworkers[5] of the first case of serum neuritis with involvement of the respiratory muscles, and of Fischer.[6]

All writers on the subject have noted the frequent involvement of the brachial plexus in serum neuritis, producing the Erb-Duchenne syndrome. According to Bennett[2] 80 per cent of cases recover completely within six months, while the other 20 per cent are left with residual muscle weakness and atrophy. Wilson and Hadden[4] regard serum neuritis as an anaphylactic phenomenon and attribute it to edema of the nerve trunks.

Because of the rarity of the disease and because this is, to my knowledge, the first case in which cortisone and ACTH were used, I am reporting the following case

CASE REPORT

D. B. M., a white male, aged twenty-seven years, stepped on a rusty nail in a barnyard at about 11 A.M. on August 12, 1951, sustaining a puncture wound of the ball of his right foot. He had been in the Army during World War II and had received immunizing doses of tetanus toxoid, with the last booster injection in 1945. There was no history of sensitivity to horses or of other allergies, and he had never been given horse serum. He came to the Accident and Receiving Ward of Presbyterian Hospital at about 8 A.M. on August 13, 1951. Examination showed a puncture wound of the ball of the right foot which was cleaned and dressed. An intradermal sensitivity test to tetanus antitoxin was markedly positive. He was therefore given the 1,500 unit prophylactic dose of tetanus antitoxin in ten divided doses of 150 units each at half-hour intervals. After the fifth dose he was also given 2 minims of 1:1000 solution of epinephrine hypodermically. Within an hour after completing the series of injections, he developed severe generalized urticaria, for which he was given 4 minims of 1:1000 solution of epinephrine hypodermically and 40 mg. of benadryl intravenously. The hives subsided but quickly recurred, so he was admitted to the hospital where treatment consisted of intravenous injections of calcium gluconate, hypodermic injections of epinephrine, benadryl by mouth and starch baths. He continued to have intermittent attacks of urticaria until August 15, 1951. He was discharged from the hospital on August 16, 1951, with instructions to take benadryl if the hives recurred.

He remained well until the afternoon of August 20, 1951, when he developed pain in the left upper arm and pain and swelling of the

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left elbow. At 4 A.M. the next day he was awakened by severe pain in the right shoulder and right upper arm, and he was readmitted to Presbyterian Hospital later that morning. Examination showed pain and swelling of the left elbow and the right shoulder, with inability to abduct and elevate the right arm. There were also paresthesias of the right arm over the distribution of the fifth and sixth cervical roots. A diagnosis of arthralgia and peripheral neuritis due to tetanus antitoxin was made. Treatment consisted of benadryl, 50 mg. four times a day, 10 cc. of 10 per cent solution of calcium gluconate intravenously daily, and codein sulfate in ½ gr. doses orally as needed for pain. However, the disease process became progressively worse during the next twenty-four hours, and signs of peripheral neuritis appeared in the left arm also. Accordingly, cortisone was started the day after admission (August 22, 1951) in doses of 100 mg. by mouth three times a day. There was immediate relief of the signs and symptoms of the arthralgia, but there was only partial relief of the manifestations of bilateral brachial neuritis. Cortisone was continued orally in doses ranging from 100 to 200 mg. daily. Oral benadryl was continued, and large daily doses of vitamin B complex were given intramuscularly. On August 28, 1951, he was seen in consultation by Samuel B. Hadden, M.D., Neurologist to Presbyterian Hospital, who agreed with the diagnosis of serum neuritis with involvement of the fifth and sixth certical roots of the brachial plexus bilaterally. As compared with previous cases he had seen, Dr. Hadden thought that this patient had been materially benefited by cortisone, and that the relief of pain and rate of improvement were unusually gratifying. Moderate improvement continued but, since the patient was not entirely cured, ACTH was substituted for cortisone on September 5, 1951, after a total dose of 2,700 mg. The initial dose of ACTH was 25 mg. intramuscularly every six hours. This was gradually reduced to 5 mg. every six hours by September 12, 1951, and was continued at this dosage until his discharge from the hospital on September 14, 1951. The total dose of ACTH was 500 mg. During the administration of this drug there was further improvement, with decrease in the pain and in the paresthesias, and increase in the movements of his arms.

Further improvement was maintained, and when he was last seen on December 27, 1951, there was practically complete recovery. Active immunization with tetanus toxoid was started on November 30, 1951, with an injection of 0.5 cc. and this dose was repeated on December 27, 1951.

COMMENTS

The continued occurrence of cases of peripheral neuritis from tetanus antitoxin further emphasizes the advisability of universal active immunization with tetanus toxoid. This patient had received tetanus toxoid during his military service but, like the great majority of ex-service men, had not kept up his immunity with booster injections. When he needed protection against tetanus, he therefore had to receive tetanus antitoxin, which resulted in serum sickness and peripheral neuritis. An antihistamine drug and epinephrine helped relieve the symptoms of serum sickness, but they did not prevent the development of peripheral neuritis. Cortisone and ACTH did not prove to be a quick cure for this complication of serum sickness, but they did hasten recovery, and may have prevented permanent damage to the involved nerves, which occurs in 20 per cent of cases. They certainly merit further trial in similar cases.

SUMMARY

1. A case of bilateral brachial neuritis due to tetanus antitoxin is reported.

2. Cortisone and ACTH were used in treatment with distinct benefit.

3. The advisability of universal active immunization with tetanus toxoid to obviate the need for prophylactic tetanus antitoxin is pointed out.

REFERENCES

1. Doyle, J. B. Neurologic complications of serum sickness. *Am. J. M. Sc.*, 185: 484–492, 1933.
2. Bennett, A. E. Horse serum neuritis. *J. A. M. A.*, 112: 590–596, 1939.
3. Richardson, W. W. Tetanus with secondary multiple neuritis. *J. A. M. A.*, 68: 1611–1612, 1917.
4. Wilson, G. and Hadden, S. B. Neuritis and multiple neuritis following serum therapy. *J. A. M. A.*, 98: 123–125, 1932.
5. Comroe, J. H. et al. Motor neuritis after tetanus antitoxin with involvement of the muscles of respiration. *Am. J. Med.*, 10: 786–789, 1951.
6. Fischer, I. Serum neuritis. *Ann. Int. Med.*, 35: 922–926, 1951.

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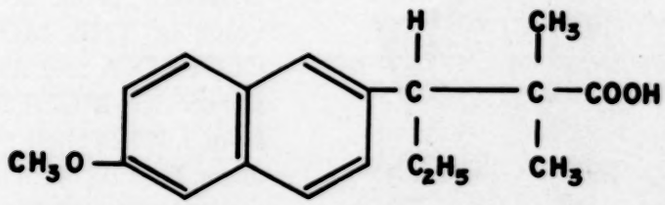

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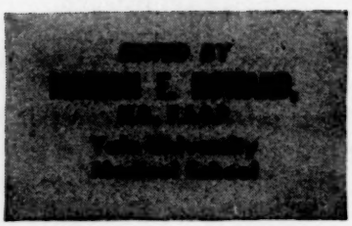

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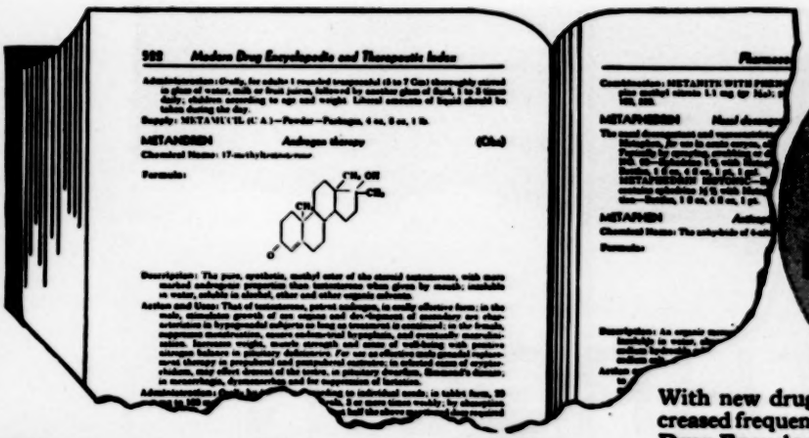

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1. McGuire et al. (1952), J. Antibiotics & Chemo., 2:281, June.
2. Heilman et al. (1952), Proc. Staff Meet. Mayo Clin., 27:385, July 16.
3. Haight and Finland (1952), New Eng. J. Med., 247:227, Aug. 14.

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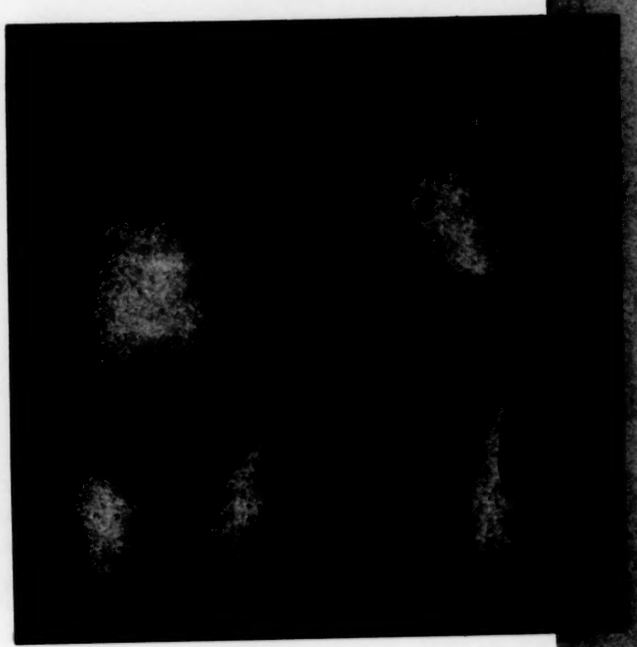

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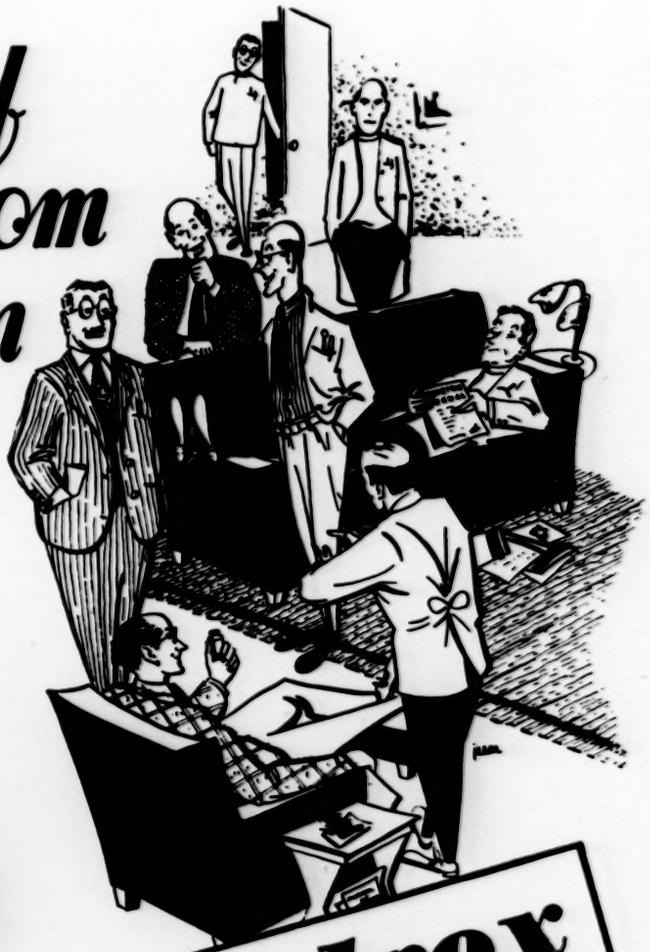

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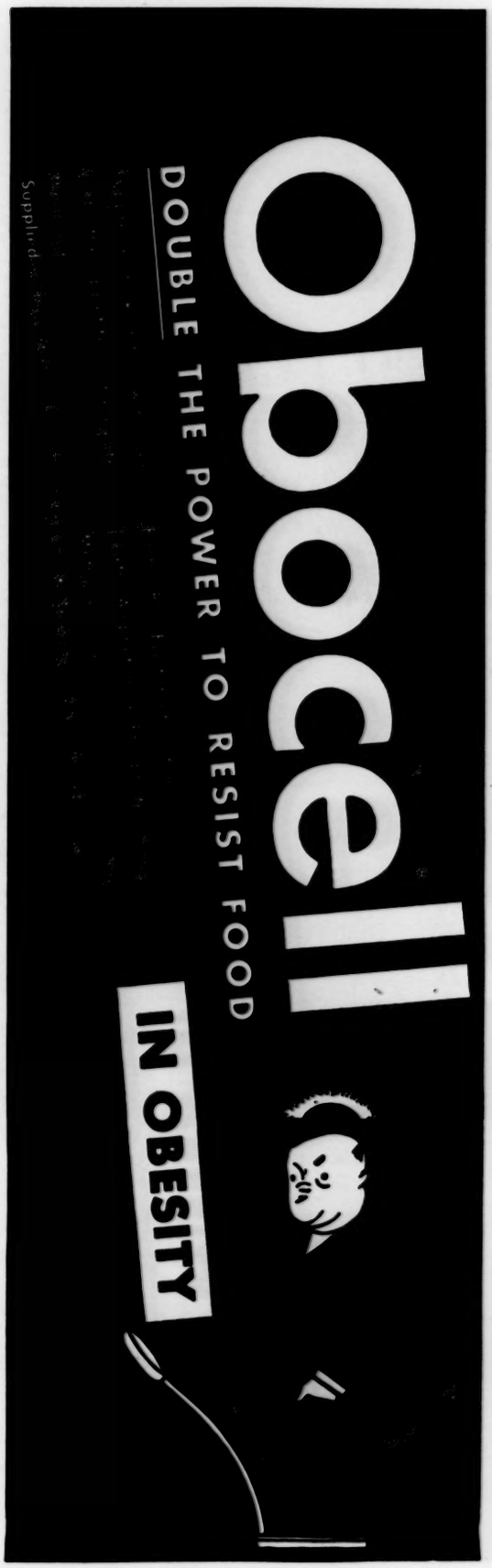

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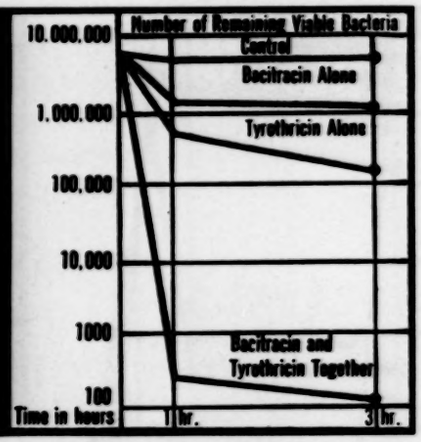

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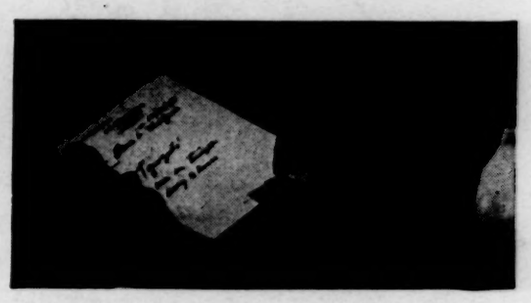

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2. Behrman, H. T., Combes, F. C., Bobroff, A. and Leviticus, R.: Ind. Med. & Surg. 18:512, 1949.

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1. Slinger, W. N., and Hubbard, D. M. (1951), Arch. Dermat. & Syph., 64:41, July.
2. Slepyan, A. H. (1952), *Ibid.*, 65:228, February.
3. Ruch, D. M. (1951), Communication to Abbott Laboratories.

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Kauntze, R., and Trounce, J.: Treatment of Arterial Hypertension with Veriloid (Veratrum Viride), Lancet 2:1002 (Dec. 1) 1951.

Wilkins, R. W.: Recent Experiences with Pharmacologic Treatment of Hypertension, in Bell, E. T.: Hypertension, A Symposium, Minneapolis, Univ. Minn. Press, 1951, p. 492.

Kauntze, R.: Medical Treatment of Hypertension, Proc. Royal Soc. Med. 45:276 (May) 1952.

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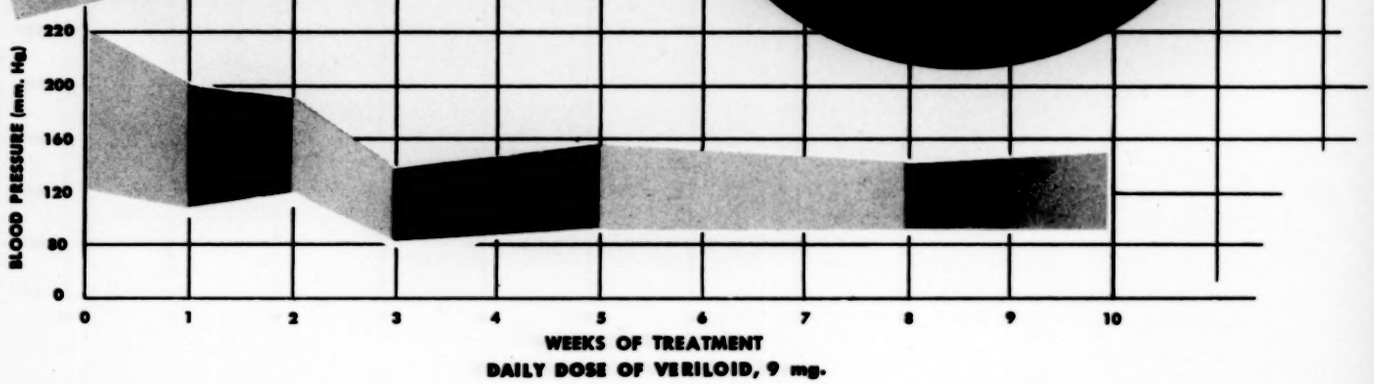

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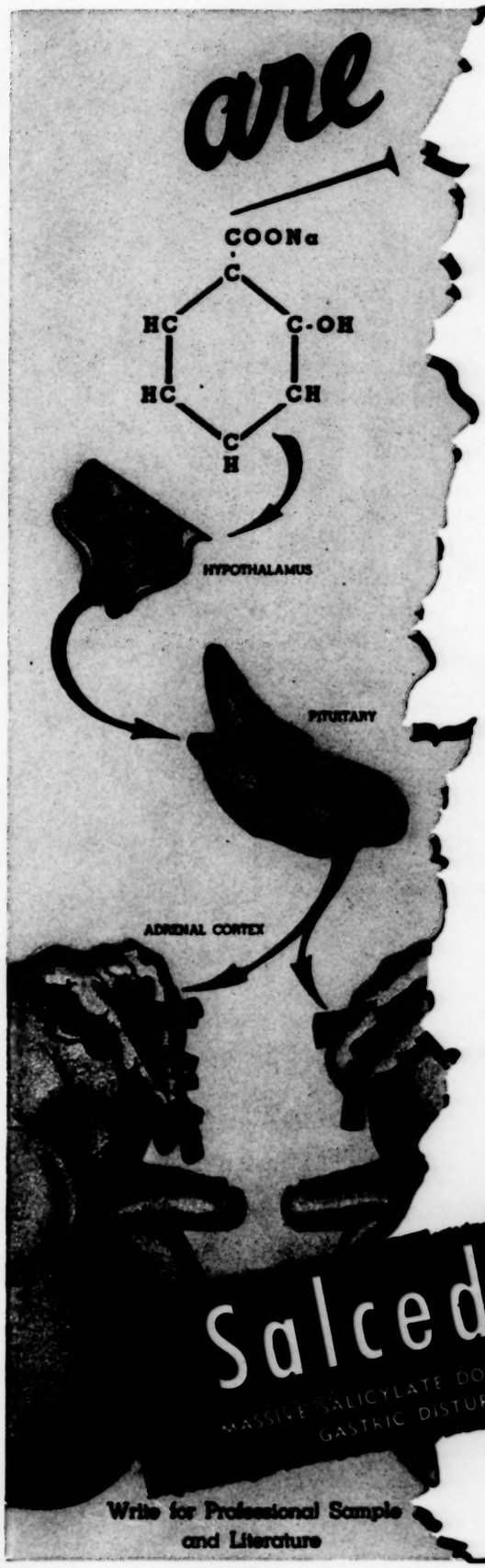

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Salcedrox virtually eliminates gastric disturbance, because of the protective combination with activated aluminum hydroxide and calcium carbonate.

Salcedrox also contains a high dose of vitamin C, because it has been observed that rheumatic and arthritic states show vitamin C deficiencies, and salicylate therapy has a tendency to intensify depletion of vitamin C.

*Proceedings Soc. Exp. Bio. Med., 1952, v80, 51-55, G. Cronheim, et al.

FORMULA

Sodium Salicylate....5 gr. (0.3 Gm.)
Aluminum Hydroxide Gel, dried ..... 2 gr. (0.12 Gm.)
Calcium Ascorbate...1 gr. (60 mg.) (equivalent to 50 mg. Ascorbic Acid)
Calcium Carbonate..1 gr. (60 mg.)

Salcedrox

MASSIVE SALICYLATE DOSAGE WITHOUT GASTRIC DISTURBANCE

Write for Professional Sample and Literature

[redacted]

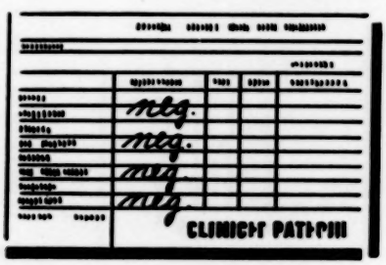
BRISTOL, TENNESSEE

Bēplete®

VITAMINS B-COMPLEX WITH PHENOBARBITAL WYETH

For the many patients who complain of nervousness, chronic fatigue, lassitude, and anorexia

in the absence of discernible organic cause . . .



BEPLETE exerts a tranquilizing effect and provides the important benefits of high dosage Vitamin B supplementation. Available as a highly palatable Elixir, and as Tablets. Also available, **BĒPLETE with BELLADONNA** for combined antispasmodic-sedative action; Elixir and Capsule forms.

Wyeth®

Donnalate

For All These Nutritional Benefits...

Constituents	Fresh Fruit, peeled	Strained Juice	Constituents	Fresh Fruit, peeled	Strained Juice
Calories	46	46	Inositol	400.0 mg.	200.0 mg.
Protein (including free amino acids*)[1,4]	1.0 Gm.	0.9 Gm.	Biotin	0.004 mg.	0.002 mg.
Fat	0.3 Gm.	0.2 Gm.	Folic acid	0.004 mg.	0.002 mg.
Dextrose and Levulose	4.0 Gm.	4.6 Gm.	Ascorbic acid (vitamin C)	60.0 mg.	57.0 mg.
Sucrose	4.0 Gm.	4.6 Gm.	Flavonoids (vitamin "P")[3]	1.0 Gm.	0.1 Gm.
Protopectins and Pectin	1.0 Gm.[3]	0.1 Gm.	Minerals (total ash)	0.5 Gm.	0.4 Gm.
Citric acid	1.0 Gm.	1.0 Gm.	Calcium	50.0 mg.	11.6 mg.
Malic acid	0.1 Gm.	0.1 Gm.	Phosphorus	30.0 mg.	20.0 mg.
Carotenes (pro-vitamin A)	1.0 mg.	0.16 mg.	Iron	1.0 mg.	0.25 mg.
Thiamine (vitamin B_1)	0.2 mg.	0.086 mg.	Sodium	9.0 mg.	6.0 mg.
Riboflavin	0.1 mg.	0.032 mg.	Potassium	150.0 mg.	170.0 mg.
Niacin	0.5 mg.	0.24 mg.	Magnesium	10.0 mg.	13.0 mg.
Pantothenic acid	0.5 mg.	0.21 mg.	Sulfur	10.0 mg.	8.0 mg.
Pyridoxine	0.2 mg.	0.08 mg.	Chlorine	6.0 mg.	6.0 mg.
			Alkalinity of ash, expressed as K_2CO_3	0.3 Gm.	0.3 Gm.

Eat An Orange...Whole...*EVERY DAY*

Good For You and Your Patients, too

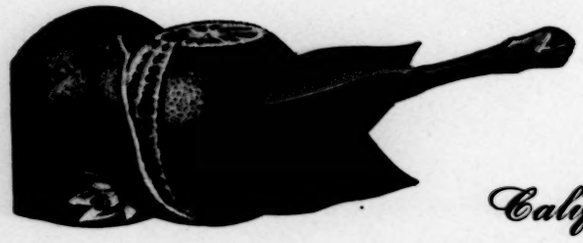
America's nationwide habit of a glass of orange juice at breakfast is well founded nutritionwise. Orange juice remains the most practical and pleasant way of insuring an adequate daily intake of vitamin C. However, valuable nutrient factors of the whole fruit are left behind when the juice is extracted.

The table shown above delineates the nutritional contribution of the whole fruit, properly peeled so as to retain what naturally clings of the albedo, the white inner peel. Virtually every essential in human nutrition is represented.

Noteworthy is the whole fruit's content of protopectins, which are found principally in the albedo, the membranes enclosing the juice sacs and segments, and the fibrovascular bundles. These nonnutritive complex carbohydrates, converted to pectin in the stomach, enhance many physiologic mechanisms. Through their colloidal, chemical and antibacterial properties, they help to maintain a desirable intestinal environment, to promote better absorption of vitamins and minerals, and to effect more normal evacuation.

Sunkist Growers • Los Angeles 54, California

California navel oranges, available all winter, are the world's finest eating oranges—no seeds, rich in flavor and vitamins. Easiest to peel, slice and section.



Sunkist

California-Arizona Oranges

ROUTINE THERAPY FOR INTERNAL HEMORRHOIDS

For the vast majority of cases of internal hemorrhoids requiring conservative treatment, the employment of RECTAL MEDICONE appears clearly indicated. The enormous prescription demand which this product enjoys, furnishes definite evidence of its value in this condition—particularly so when prompt symptomatic relief is vital for the comfort and well-being of the patient.

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More than 10 years of research, plus experience of practice in thousands of cases, are combined to bring your hypertensive patients the best therapeutic benefits of Veratrum viride when you prescribe Veratrite®.

These benefits are (1) prolonged fall in both systolic and diastolic blood pressure without postural hypotension; (2) improved circulation to vital organs; (3) effective control of patients through years of sustained therapy; (4) complete safety with simplicity and economy of administration.

Each tabule contains:
Whole-powdered Veratrum Viride (Irwin-Neisler) . . . 40 C.S.R.* Units
Sodium Nitrite . . . . . 1 grain
Phenobarbital . . . . . ¼ grain
*Carotid Sinus Reflex

Veratrite

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AQUASOL A CAPSULES
is the first and only product to provide water-soluble natural vitamin A in capsules . . . and is made by the "oil-in-water" technique developed in the Research Laboratories of the U. S. Vitamin Corporation (U. S. Pat. 2,417,299).

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25,000 U. S. P. Units
natural vitamin A per capsule
. . . in water-soluble form

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natural vitamin A per capsule
. . . in water-soluble form

advantages:

up to 500% greater absorption
80% less excretion
85% higher liver storage

indications:

for more rapid, more effective therapy in all vitamin A deficiencies . . . particularly those associated with conditions characterized by poor fat absorption (dysfunction of the liver, pancreas, biliary tract and intestines; celiac and other diarrheal diseases).

Proven effective in ACNE and other dermal lesions responsive to high potency vitamin A.

Bottles of 100, 500 and 1000 capsules

Samples upon request

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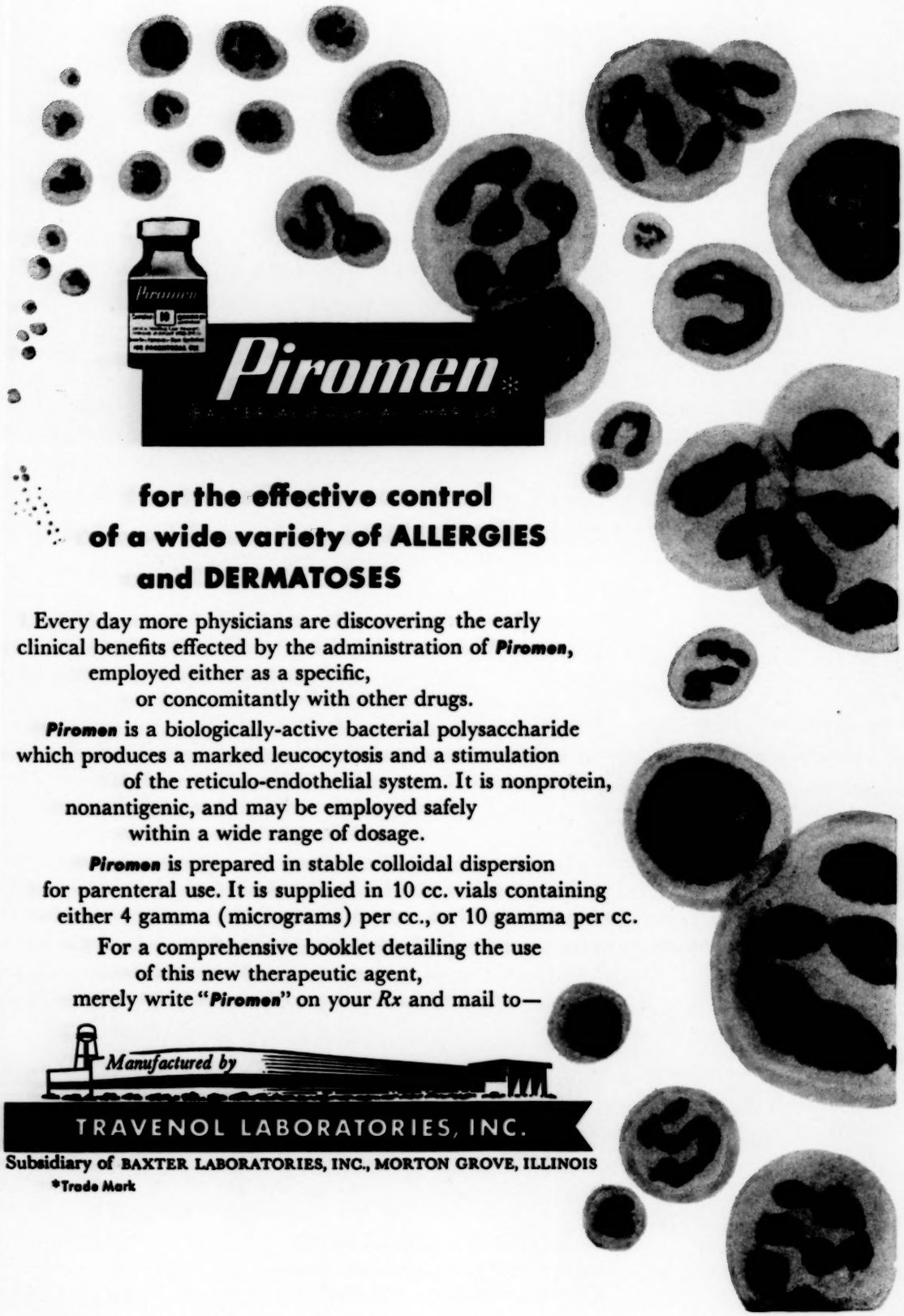

for the effective control of a wide variety of ALLERGIES and DERMATOSES

Every day more physicians are discovering the early clinical benefits effected by the administration of ***Piromen***, employed either as a specific, or concomitantly with other drugs.

Piromen is a biologically-active bacterial polysaccharide which produces a marked leucocytosis and a stimulation of the reticulo-endothelial system. It is nonprotein, nonantigenic, and may be employed safely within a wide range of dosage.

Piromen is prepared in stable colloidal dispersion for parenteral use. It is supplied in 10 cc. vials containing either 4 gamma (micrograms) per cc., or 10 gamma per cc.

For a comprehensive booklet detailing the use of this new therapeutic agent, merely write "***Piromen***" on your *Rx* and mail to—

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